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In the issue of January 29 of the *New England Journal of Medicine* there appeared an editorial on National Heart Week, February 8–14. In part, it said:

"Nearly every physician is aware, from his day-to-day practice of medicine, that a gross disproportion exists between the amount of time and effort spent on research in cardiac diseases and the frequency of their occurrence in his practice. Without any deprecation of the research being done in other fields, it must be acknowledged that the actual problems the family physician faces day in and day out in a very large number of patients are those of hypertension, arteriosclerosis and valvular heart disease.

"Perhaps some of this disproportion in public interest and support of health programs has been the fault of the medical profession. Too often laymen have been permitted to develop public interest on an emotional rather than a factual basis. Physicians therefore welcome a program for public understanding and fund raising that is professionally inspired and directed, such as the program of the New England Heart Association, which will be publicized during National Heart Week, February 8–14."

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Journal of Medicine

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MEDULLOBLASTOMA CEREBELLI*

Diagnosis, Treatment and Survivals, with a Report of Fifty-Six Cases

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BOSTON

SINCE the first description of medulloblastoma cerebelli was published by Bailey and Cushing[1] in 1925, this rapidly growing tumor of the cerebellum has been recognized as occurring most often in children and leading to the abrupt onset of increased intracranial pressure and cerebellar dysfunction. Evidence has accumulated, however, that this typical syndrome is not always found in patients with medulloblastoma cerebelli and also that certain other tumors of the cerebellum give clinical symptoms indistinguishable from those of medulloblastoma. It is well known that medulloblastomas are much more successfully treated by irradiation than by radical extirpation. The place of surgery in the treatment of medulloblastomas, the amount of x-ray therapy desirable and the results to be expected are still open questions. We are therefore recording our experiences with medulloblastoma cerebelli with particular reference to the results obtained with various forms of treatment.

The series is composed of 56 patients from the following sources: patients seen at the Peter Bent Brigham Hospital since 1930, some of whom had originally been treated before that date in Dr. Cushing's clinic; and all the patients in the records of The Children's Hospital, many of whom were transferred to the Peter Bent Brigham Hospital for treatment before 1930. For this reason, some of these cases have already been reported elsewhere by other authors.[1–12] We have excluded from the series examples of the so-called "cerebral medulloblastoma," since it is not certain that they are identical pathologically with cerebellar medulloblastoma and since the clinical behavior of these two types of tumor is entirely different. Although medulloblastoma cerebelli is largely a tumor of childhood, evidence that it occurs in adults more often than was previously thought is accumulating.[12–14] In all cases the diagnosis of medulloblastoma cerebelli in this series has been based on histologic identification, and sections of each tumor have been reviewed to exclude any not conforming to the present concept of this lesion. The specific anatomic locations are shown in Table 1. It is interesting to note that 15 of the 56 tumors did not occupy the classic midline position in or above the fourth ventricle.

Some authors[6] have believed that a difference exists between tumors arising in the midline, in the lateral cerebellar hemispheres and in the cerebellopontine angle or in the pons itself. In our series there were no apparent differences in the natural history of the tumors in these sites. The only objective finding that varies in these locations is the average age of the patients; the ages were higher with pontile tumors than in those of the cerebellum (Table 1). However, the numbers involved are so small that the statistical significance of the difference in age is doubtful.

The distribution of all patients in the series according to age is in agreement with other reports. Twenty-four were in the second five years of life, and forty-two were in the first decade; but typical tumors were also seen in patients as old as thirty-seven and sixty-five years.

Distribution by sex was about equal; there were 31 males and 25 females.

Symptoms had been present on the average for slightly more than three months before the patient was brought to the hospital. The patient seen earliest after the onset of symptoms had noticed difficulty for only a week, and the longest prehospitalization period was twenty-four months. This is in agreement with the experience of many other clinics that the onset of symptoms in medulloblastoma is usually, but not always, rapid and that the symptoms follow a pattern of disturbed cerebellar function and increased intracranial pressure. It should be pointed out that medulloblastoma is

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not the only tumor in the posterior fossa that causes abrupt onset of symptoms. Tumors that are much lower in malignancy and far more satisfactorily treated surgically sometimes give rise to clinical pictures indistinguishable from those due to medulloblastoma. For this reason, we believe it to be of the utmost importance to make a biopsy in each patient before roentgenotherapy is begun.[11]

Sixty explorations of the posterior fossa were carried out on 53 patients in this series. In 3 cases surgery was regarded as inadvisable in view of the condition of the patient. Biopsies were made in the course of these explorations. When larger portions of the tumor were accessible and could be extirpated without additional risk to the patient, this was done. In 3 patients it was necessary to expose medulloblastomas of the cerebellopontine angle through an occipital craniotomy after the suboccipital approach had failed to give adequate exposure. In 6 patients burr holes were made as procedures separate from a surgical approach to the tumor.

When the circulation of the cerebrospinal fluid was not re-established with certainty by removal of tumor or by freeing of adhesions, some further procedure was necessary to protect it. A tube was inserted for this purpose by the method of Torkildsen[15] in the course of seven of the sixty posterior-fossa explorations. The tube used in recent operations was made of polyethylene,[16, 17] which causes less tissue reaction than the rubber catheters formerly employed for the purpose. In 3 other patients third ventriculostomies were carried out as separate procedures, a right frontal approach being used. We prefer to use third ventriculostomies for older patients, but they have not been so successful in younger ones because the opening often closes after a time. It is our impression that these operations have given the patients a maximum period of freedom from symptoms followed by a rapid downhill course in the terminal phases.

In all, seventy-two operations were performed on 53 patients, with an operative mortality of 32 per cent.*

It has long been recognized that the medulloblastoma is more prone than any other glioma to extend to the meninges and to produce secondary deposits within the cerebrospinal axis. The occurrence of metastases was demonstrated in 19 cases (Table 2). Of these, 10 showed distant spinal or cerebral seedings; the remaining 9 were local subarachnoid extensions. It is possible that the operative procedure is at times responsible for the dissemination of tumor particles. That this is not the only means of subarachnoid spread is shown by 2 cases in which metastatic implants were seen at the time of the first operation.

Not all these metastases caused definite symptoms; in 2 cases, however, a definite paraplegia was present. Cord bladder occurred in 5 cases, and 7 patients complained of severe pain in the distribution of spinal segments, which could be explained by no other cause (Table 3). One patient was even subjected to a laparotomy because of persistent right-lower-quadrant pain. This same child's death was ultimately due in large measure to transection of the spinal cord by tumor.

Another complication was acute gastric ulceration, which occurred in 3 patients (Table 2). In only 1 of these cases were the perforation and extent of the resulting hemorrhage and peritonitis sufficient

TABLE 1. *Locations of Medulloblastoma Cerebelli in 56 Cases.*

POSITION	NO. OF CASES	AVERAGE AGE
		yr.
Midline	41	7.5
Pons and cerebellopontine angle	10	16.1
Cerebellar hemispheres	5	7.5

TABLE 2. *Complications.*

COMPLICATION	NO. OF CASES	NO. OF DEATHS
Metastases	19	2
Distant spinal or cerebral	10	
Local extension	9	
Acute gastrointestinal ulcerations	3	1
Postoperative intracranial hemorrhage	3	3
Wound infections	2	1
Bronchopneumonia	2	2

TABLE 3. *Clinical Symptoms Related to Metastases.*

SYMPTOM	NO. OF PATIENTS
Somatic pain	7
Cord bladder	5
Complete paraplegia	2
Horner's syndrome	1

TABLE 4. *X-Ray Dosage and Survival Time.*

X-RAY DOSAGE	NO. OF CASES	AVERAGE SYMPTOM-FREE INTERVAL	AVERAGE TOTAL SURVIVAL
r		mo.	mo.
Undetermined	6	2.6	7.4
None	17	0	0.3
150–2850	9	4.6	7.6
4500–9600	15	24.0	31.6
10800–30000	9	44.6	54.0

*Following Cushing's precepts,[9] we regarded any patient who died in the hospital during an admission in which an operation was performed as an operative death, although in some cases the cause of death was unassociated with the immediate operative procedure.

to be regarded as the cause of death. All 3 cases of postoperative intracranial hemorrhage were fatal. The only 2 cases of bronchopneumonia that were diagnosed at autopsy were terminal, but not agonal, and cannot be considered the sole cause of death. Of the 2 cases of wound infections, 1 was a fulminating streptococcal meningitis, which was fatal on the third postoperative day. The other was a slight infection of the superficial layers of the wound, which proceeded to heal well after only a brief delay.

Experience has shown that x-ray therapy is by far the most effective treatment for medulloblastoma cerebelli. Three patients in the series died before the institution of definitive treatment. Fourteen more patients were operated upon but did not receive roentgenotherapy in the early part of the series before modern therapeutic radiation was available. The majority (39 patients) were operated on and received therapeutic irradiation in addition. There were 9 patients still living on January 1, 1946 — a case mortality of 84 per cent.

The survival of all patients is shown in Table 4, together with the amounts of roentgenotherapy received, and with an estimated "symptom-free" period of survival. These periods of survival are calculated from the date of the first hospital admission. The termination of the "symptom-free" period is based on purely subjective estimates from correspondence and outpatient records and has no objective criteria. It is the prolongation of this period, however, that is the chief goal toward which our therapeutic measures have been directed.

Six of the patients treated received undetermined amounts of roentgenotherapy; in 10 other cases completely accurate figures are not available, but figures representing minimum known dosages are used. In the remaining 23 patients, the dosages are known to be accurate.

Only 1 patient who received less than 4000 r of total therapy survived more than fourteen months, the average survival being slightly under eight months (Table 4).* One of these patients was still living fourteen months after admission, but was in a nursing home for terminal care.

Fifteen patients received between 4000 and 10,000 r, with an average survival time of thirty-one and a half months. If the patient who survived for twenty-two years[12] is excluded, the average survival time falls to fourteen months. The average survival of all the patients who have died is seventeen months; the average "symptom-free" period of these same patients is slightly more than eleven months; excluding the patient who survived twenty-two years, this is lowered to nine months.

None of the patients who received more than 10,000 r is still alive, but the average survival period is fifty-four months, the least being seventeen months and the greatest being slightly over twelve years. The "symptom-free" survival in this group is over forty-four months. It must be recognized, however, that although the larger dosages of irradiation may be assumed to be the cause of a longer survival, it is also true that only in those patients who lived for a fairly long time after admission could such large dosages be accumulated.

Several of these patients received unusually large total dosages over the course of several years, the highest being approximately 30,000 r to the skull and spine over three and a half years. Some authors[18] have doubted the advisability of using such large dosages of therapeutic irradiation and have published reports of degenerative changes when dosages between 10,000 and 15,000 r had been used. In no cases in this series were any similar degenerative changes ascribable to roentgenotherapy specifically noted.

Systematic records of responses to x-ray therapy are not available on several of the patients with spinal metastases; 4 cases with adequate records demonstrated at least some response to therapy — in 1 case almost complete remission of pain for four years.

TABLE 5. *Causes of Death.**

CAUSE	NO. OF PATIENTS
Increased intracranial pressure	20
Increased pressure, local edema, shock	9
Postoperative hemorrhage†	3
Meningitis	1
Accidental	1
Shock†	1
Metastases	1
Undetermined	11

*The number of living patients is 9.
†One patient also had an upper intestinal ulceration.

The clinical difficulties due to the irradiation were leukopenia, vomiting and acute cerebral edema. In 6 cases treatment was interrupted because of leukopenia (this occurred twice in 1 patient). Vomiting followed the irradiation in most patients, but in only 1 case was it of such magnitude as to require cessation of treatment. One patient died of cerebral edema after one treatment of 150 r. Autopsy showed a very edematous brain, with a marked pressure cone. The child also had an acute gastric ulcer, but this was not regarded as an important factor in the fatal outcome, since there was no evidence of perforation or bleeding from the ulcer at autopsy.

Tabulation in terms of survival periods without consideration of form of therapy reveals that there are 7 cases of three years' survival (12.5 per cent). Of these, only 3 went on to the five-year mark (5.4 per cent); 2 patients survived more than ten years (3.6 per cent). One of the last is still living

*In calculations of these survivals, only the patients who lived to receive any roentgenotherapy are included.

and in fairly good health twenty-two years after her original admission.[12]

Table 5 shows the causes of death in the entire series. Placed together are 20 fatal cases that can be ascribed almost entirely to one factor — increased intracranial pressure. Nine other deaths may be attributed to a combination of increased pressure, local edema, local trauma, local extension of the tumor and peripheral shock. In 11 cases no definite cause of death could be assigned, the patients having died outside the hospital.

Since the patients reported in this series have been treated by more than one neurosurgeon and over a long period, the forms of therapy used have varied considerably. On the basis of this experience our present choice of treatment has been exploration as soon as the diagnosis of a posterior-fossa tumor is made. Temporization with preliminary trials of roentgenotherapy does nothing but jeopardize the vision of children who have a benign cerebellar tumor.[11] If, at operation, it is possible to remove more than enough tissue for a biopsy, a larger portion of the tumor is resected, and a means for circulation of the cerebrospinal fluid is provided. As soon as the wound is healed, the patient is given an intensive course of roentgenotherapy, not only to the cerebellar area but also to the spine, in an attempt to destroy any metastatic seeding that may already be present. This first course of irradiation usually amounts to a total of 5000 r. It is followed in six months — sooner if the symptoms warrant it — by more irradiation through cerebellar portals. If there is evidence of spinal involvement, appropriate roentgenotherapy to the spinal portals is instituted. Re-exploration is indicated in the presence of obstruction to the circulation of cerebrospinal fluid, and an attempt to short-circuit the flow, by a tube as suggested by Torkildsen[15] in younger patients or by a third ventriculostomy in older patients.

Summary

Fifty-six cases of medulloblastoma cerebelli are described, and the results obtained by various forms of therapy evaluated. It is of great importance to establish histologic proof of the presence of medulloblastoma before roentgenotherapy is begun. Short-circuiting operations for the relief of increased intracranial pressure have been of considerable assistance in selected cases. Vigorous treatment of cerebellar medulloblastomas with irradiation is always indicated. Even if permanent cure can rarely be accomplished, it is possible to prolong a relatively "symptom-free" period of survival, which may then be followed by a brief downhill course.

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THE PRACTICAL IMPORTANCE OF MODERN CONCEPTS OF PSYCHOSOMATIC RELATIONS*

ALFRED O. LUDWIG, M.D.†

BOSTON

THE term psychosomatic in its present-day usage serves commonly to designate a group of diseases with organic changes in which emotion is thought to play an important etiologic role. It is unfortunate, however, that there is a tendency to think of this approach as constituting still another specialty within the body of medicine. It would be far healthier if a broader concept could be adopted in which the attempt to study and describe both the physical and emotional aspects of illness could be viewed as a step toward the unification of all medical knowledge as it pertains to disease in a patient.

The recent investigations in this field are an approach toward incorporating into the structure of medical science what used to be known as the art of medicine. Everyone is familiar with the consummate skill of the experienced general practitioner, which combined a detailed personal knowledge of the patient, his past life and his family with sound medical understanding as well as a great intuitive grasp of emotional problems and a warm friendly support. Striking therapeutic success and an excellent doctor-patient relation were often the result. However, these efforts could never be more than intuitive or empirical, nor could they be made predictable or manageable until they were subjected to careful psychiatric investigation.

To consider the patient as a person one must first accept the reality of emotional reactions. For example, one should not forget that nausea and vomiting may be caused entirely by strong emotions as well as by structural changes or by irritating substances in the stomach. Somewhat more difficult to visualize but now well established is the concept that emotion can eventually produce structural changes in the body. Once this is admitted a far broader view of the nature of disease must follow. It is vital that the patient be made to feel that he — and not his body alone — is the focal point of the doctor's interest.

From this it follows that psychogenic illness or any disturbance in which one cannot demonstrate organic change should no longer be considered as imaginary or even perhaps as consciously planned by the patient in an effort to deceive. Such an attitude defeats therapy before it begins. It brands the patient as a liar and denies the existence of his symptoms. One must make certain that the patient's feelings, his personal relationships, his life situation and his reaction to his environment are all subjected to the same painstaking scrutiny as his physical body and its symptoms. His emotions should be examined with the same objectivity as his organs, and here it is well to caution that moral judgment regarding behavior has no place in medical treatment. Irritating or annoying actions can be as much a part of a pathologic picture as organic disease and should receive from the doctor the same dispassionate appraisal, never unreasoning retaliation.

The first group of disorders of importance to the practicing physician are neuroses that manifest themselves by somatic disturbances, such as gastrointestinal, cardiovascular and skeletal symptoms. It has been estimated that from 30 to 50 per cent of all the patients seen in medical outpatient clinics are of this type.

It is highly important that such patients be handled properly from the outset. This implies that one take a careful medical history, which should include at least an attempt to outline the gross personality traits as they pertain to the illness. An adequate physical examination should follow, with special attention to the part of the body that is the seat of the complaint. Necessary laboratory work should be done when indicated.

At this point the physician can make or break the successful treatment of the case. If no significant organic changes are demonstrated, the patient should be so informed and should then be instructed, in the simplest words, concerning the mechanism of production of psychogenic symptoms. It is well not to use ambiguous or unfamiliar terminology and to be as definite and precise as possible, lest misapprehension arise. For example, many a patient becomes "heart conscious" and develops or perpetuates cardiac symptoms after injudicious remarks, too prolonged attention to examination without explanation or overemphasis upon nonsignificant findings such as murmurs and disturbances in rhythm. It is well always to minimize when possible, especially with these apprehensive patients. An evaluation of the patient's personality will give valuable clues regarding how much and what he can be told in such situations. All explanations should be clear and concise, and the patient should be encouraged to ask questions to allay any fears that he may have. Such care takes little extra time and results in very valuable therapeutic effects.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1947.

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If the disease is purely psychogenic, treatment should not be organic. Every neurotic person seeks to evade responsibility by falling back upon an organic diagnosis. It is more comfortable and more acceptable to explain symptoms as due to alien infections or other external causes than to accept personal responsibility as one must if one's own emotions, be they conscious or unconscious, are at fault. In this respect the experiences with such disorders during the war gave valuable information. Disability from acute somatic symptoms, which were due largely to emotional causes, was common in infantry soldiers under fire. When such men were asked for their explanation of the origin of their disturbances most were prone to blame external agents, few admitting that fear had played any part in making them ill. In this situation, an organic illness furnished an honorable way out in which fear had no part. A recognition of this chain of events and explanation of the psychologic aspects salvaged many useful soldiers for further action when it was accomplished soon after the onset. However, if the doctor made the error of accepting the patient's explanation of an organic external agent as the sole cause of his illness, he supported his rationalization and provided the neurotic process with the needed justification. All these men felt great guilt at leaving their buddies. The longer they were hospitalized, the greater the guilt and consequent need for further justification. Under such conditions recovery was greatly hampered and indeed often became impossible. Although such extreme pressures do not pertain to civilian patients, the underlying principles are the same, and the same precautions must be taken.

Unnecessary surgical procedures are especially harmful. In the presence of severe neurosis, the patient may often unconsciously seek such treatment in part as punishment for severe guilt feelings. Unless the indications are very clear-cut or an emergency exists, surgical procedures are best avoided in the presence of evidence of hysteria or other severe neurosis. Grave errors have been made in such situations with the newer operations to relieve pain. Such unwarranted interference not only has failed to give relief but also has too frequently led to repeated surgical measures that made eventual psychiatric care much more difficult.

There is no doubt that there is still a large group of patients in whom persistence of disability must be blamed on the injudicious medical management of psychogenic symptoms. Such cases are unnecessary and preventable. Usually, the treatment does not require specialized psychiatric knowledge. Adherence to the simple principles of considering the patient as a person, adequate examination, avoidance of unnecessary diagnostic procedures, simple explanation and reassurance usually suffices to alleviate or remove the symptoms and to restore self-confidence. In severe cases, of course, specialized psychiatric treatment must be utilized.

Another important category of illness is made up of disorders in which recent studies have shown that emotional influences acting over longer or shorter periods result at first in disturbed physiology and eventually in structural change. Peptic ulcer is the simplest example. In this condition disturbed emotions lead to hypersecretion of gastric hydrochloric acid. When this has persisted long enough under certain conditions actual ulceration supervenes. Ulcerative colitis is another serious disorder in which emotional factors play an important role. In both these diseases dangerous complications and even death are not infrequent. Other disturbances in this group are the allergic illnesses such as asthma, hay fever and urticaria, certain skin diseases, such as eczema and neurodermatitis, migraine, possibly certain cases of epilepsy; hypertension and rheumatoid arthritis.

Addiction to alcohol and to drugs has long been considered a purely psychiatric disorder. Another addiction — namely, that to food, — which leads to simple exogenous obesity and which may result in the complications that are secondary to pathologic accumulations of fat, has been shown to have important psychologic aspects.[1, 2]

There seems to be emerging slowly a clearer understanding of the personality structure of persons who become ill in this way or who react with their bodies to certain emotional crises. These patients, usually unbeknown to themselves or others, appear to have remained or to have been pushed back to extraordinarily primitive and early stages of emotional behavior. They manifest an extreme degree of dependence upon certain key figures around them. This dependence on closer survey turns out to be so exaggerated that it suggests an almost symbiotic relationship. The loss of these key persons by death or by separation produces catastrophic helplessness and is often followed by organic illness. Lindemann[3] has reported that in 33 of 41 cases of ulcerative colitis, the disease began after the loss of important persons in the patient's life. The onset of rheumatoid arthritis after the death or illness of close relatives has frequently been reported in the past[4, 5] and has been observed in a small group of carefully studied patients.[6]

This extreme degree of insecurity and need for the support of others is manifested in various ways. It may be displayed openly as a childish, clinging, extremely demanding and grasping attitude with marked impatience and intolerance to any discomfort. On the other hand it may be completely hidden. In this event only the defense against the underlying weakness is seen in the form of an exaggerated false front of self-reliance and independence. The inadequacy of this defense becomes apparent when it collapses before any event that forces the patient into a dependent attitude. Such an event may be

the loss of economic status, the loss of key figures or separation from the family, a group or even a familiar environment. Loss of body substance or parts of the body, by injury or by operation, may also be a precipitating event. Apparently, many of these persons are extraordinarily dependent on the constant presence of outside help for the maintenance of security and psychologic integrity.

Coupled with this extreme degree of dependence is an exaggerated intensity of emotion. In consequence, these patients become extremely controlled outwardly and are usually considered to be cold and unfeeling. They fear any loss of control because it may result in an explosive and overwhelming outburst. It is as if they could express this intensity only through the channel of bodily symptoms.

Contact is difficult and they tend to live in isolation. Personal relations are difficult except on a superficial level. Their greatest fear is that of complete helplessness. Organic illness brings some recompense in that it is accompanied by the security secondary to attention and medical care. However, so great is the fear of relying on others, paradoxically, that the patients may actually resist treatment. It is not infrequent to find this reaction in patients with rheumatoid arthritis, who persist in activity even though they know they should be in bed. Resistance to the effect of drugs — that is, to being controlled by them — is another idiosyncrasy that is occasionally observed.

Eating is one primitive method of solving difficulties employed by these patients. For them, eating can assuage a sense of loss, of depression or of deprivation, and on the other hand it may serve to relieve anger or rage. At times it seems as if any discomfort can be relieved by this means. It is interesting that eating disturbances are not infrequent in such patients. Large fluctuations in weight, from obesity to pathologic weight loss, are common in the histories. Oral drug addiction is not rare, and one need recall only the very troublesome craving for tobacco that appears in certain patients with peptic ulcer, as well as the propensity for drug addiction in patients with rheumatoid arthritis even in the absence of a significant degree of pain.

These patients appear to have extremely loosely organized personalities. Their self-confidence is easily shattered by any deprivation or loss, whether of support from the outside or of a part of the body by injury or operation. They are greatly dependent on outside help and react to insecurity with violent emotions. Responses are primitive and of total intensity. In this primitive stage such strong emotions are expressed by physiologic changes rather than by the more mature methods of physical activity, the outward expression of feeling or by verbalization.

What are the implications for treatment? To influence such patients, it is essential to establish contact with them. This requires a very warm, friendly and giving type of approach, such as is usual and customary for the practitioner of medicine. It has been shown that therapeutic efforts may be defeated by the use of the passive psychiatric technic of exploration, which requires that the patient give a great deal of himself in words and ideas while receiving little in return.[3] Such efforts make demands on these patients of which they are incapable, and they are resisted with silence and hostility. They may result in actual exacerbation of bodily symptoms.

Every known therapeutic device must be utilized to demonstrate the doctor's interest and his willingness to help. This may be aided by attention to every detail of comfort and care from the medical, nursing and psychologic points of view.

It will be clear that such vulnerable persons will be suspicious and distrustful, and therefore it is vital that an attitude of extreme honesty be maintained at all times. If mistakes are made, they must be freely acknowledged. Strong support and reassurance are essential, and it is often necessary to infuse one's own optimism, confidence and strength of will into the patient. This he accepts by identification. The doctor may have to put himself temporarily into the role of the lost key figures or seek to manipulate the environment so that they are replaced.[3]

One must never try to push these patients too hard or too fast. Pressure is felt as rejection and hostility and either is strongly resented or produces exacerbation. One must avoid becoming annoyed by demanding and grasping attitudes. Often, these persons deliberately try one's patience by overt hostility. It is best to inquire into the reasons for such behavior, before retaliating. Many of them suspect that the entire world is hostile and cannot believe that anyone has any good intentions. The best results are obtained by gentle suggestion. One should attempt by every means to produce a therapeutic situation in which doctor and patient cooperate toward rehabilitation.

Restoration of maximal working efficiency should be a therapeutic goal equal to cure or alleviation of the disease itself. Emotional factors that may contribute to the dependency should be explored and removed whenever possible. Social service, by investigating and lightening the burden of family and environmental stresses, has much to offer. Occupational therapy should be so organized that it uses methods commensurate not only with the patient's physical ability but also with his intellectual and vocational aptitude. Under such conditions it can greatly assist rehabilitation. Vocational guidance, with retraining when indicated by the limitations of illness, deserves a larger place in organized medicine. Greater utilization of every facility available in the hospital and elaboration of

the concept of the therapeutic team should add greatly to the speed of rehabilitation.

A word regarding the role of compensation and pension in disease is indicated. The justice and humanity of the principle of compensation for injury or illness sustained in industry or war are freely conceded, but a much greater understanding of the insidious and highly crippling effects of a continuing pension must become more widespread among the medical profession. Everyone has seen patients pushed into and maintained in chronic invalidism through the payment of weekly or monthly pensions. Especially if he is already insecure, the patient clings to his pension as his only lifeline, which although it is pitifully inadequate, protects him from complete helplessness. He is afraid to take steps toward independence even when there are no longer adequate physical reasons for disability because of the fundamental loss of self-confidence secondary to his illness. By the same token he cannot give up his only prop of compensation. Such behavior is neither conscious nor deliberate but represents a secondary neurotic dependency that is nurtured by the continued pension. From the point of view of rehabilitation, continuing compensation is not humane but hampers recovery. A review of present attitudes toward these practices is necessary, and lump-sum settlement offers one possibility for a solution.

Recent advances in the treatment of acute infectious disease have greatly decreased the dangers and economic loss from these illnesses. This requires that even greater attention be given to the large group of chronic and disabling diseases. If the patients are to be rehabilitated, the emotional relations that enter into the causation and treatment of their disease must receive much more study and consideration, and this knowledge must become part of the thought and practice of every doctor.

In certain clinics in this country the psychiatric service has placed representatives in every outpatient clinic, surgical or medical.[7] Such close working together with every specialty has greatly furthered the understanding of the emotional aspects of illness in every special field and has made psychiatric knowledge much more available throughout the hospital. A wider application of such co-operation is to be welcomed.

It is likely that a new approach will have to be found to teach medical students these aspects of disease. Descriptive psychiatric teaching has its place, but it appears essential for every medical student to understand fully the psychologic development and the personality structure of normal as well as abnormal persons. It would be well if such teaching became an integral part of the entire medical curriculum.

Only complete consideration of all aspects of every patient and his illness — physical, emotional or environmental, and no matter in what special area of medicine — can eventually give an adequate understanding of the true mechanisms of disease and the most efficient and rational treatment.

101 Bay State Road

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THE CYTOLOGIC METHOD IN THE DIAGNOSIS OF CANCER*

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BOSTON

TO MAKE a balanced judgment is always difficult. It is a human failing to see things either black or white and, often with insufficient evidence, to render an immediate and final decision either for or against. We shall describe a new test for cancer and present evidence of its value. It is not our contention that this new test should compete with biopsy or replace that method in the diagnosis of cancer. The electrocardiograph did not supersede the older methods of diagnosis in the detection of diseases of the heart. The eyes, the ears and the hand still remain the tried means of evaluating the cardiac state. Nevertheless, the electrocardiograph not infrequently reveals the presence of myocardial changes incapable of detection by the unaided senses, and it has become an essential aid in the interpretation of many cardiac conditions. The diagnosis of cancer by cytologic examination of body fluids bears a similar relation to diagnosis by the older methods. Not infallible, the new method nevertheless supplements the biopsy and in some cases gives information that the biopsy cannot give. Just as the electrocardiograph is now an indispensable aid in cardiology, so we consider the cytologic examination an essential complement to biopsy in the diagnosis of cancer.

Diagnosis by the cytologic method depends upon the fact that malignant tumors upon any free surface desquamate tumor cells into the surrounding medium. We are familiar with the continuous desquamation of normal cells, as evidenced by the constant presence of squamous cells in the vaginal secretion, the sputum and the urine. There is some evidence that the surface cells from malignant tumors desquamate even more rapidly than normal cells of similar origin.

For many years pleural and ascitic fluids have been examined for malignant cells, their presence depending upon the same property of desquamation. The method was first made applicable to other than metastatic tumors by Papanicolaou, who, in 1928, recognized cancer cells in the vaginal secretion of women with cancer of the uterus and on the basis of this observation published in 1941 the description of a new method of diagnosis of uterine cancer.[1] A detailed technic of the vaginal-smear method has been described.[2–4] Briefly, a dry pipette with a capillary opening and capped by a rubber suction bulb, is introduced into the posterior vaginal fornix; the bulb is released, and the pipette withdrawn. The aspirated fluid is blown upon a previously marked glass slide, immediately fixed in equal parts of ether and 95 per cent alcohol, stained and examined for cancer cells. Criteria for the recognition of such cells is found in the articles to which reference has been made. Only after long experience may cancer cells be confidently distinguished from the many types of normal cells present in the vaginal secretion.

The value of this diagnostic method has been well established. Papanicolaou's[5] original report has been confirmed.[6–8] In a controlled study Hertig[9] obtained positive smears in 39 of 40 cases of carcinoma of the cervix and in 15 of 18 cases of carcinoma of the fundus. Eight positive and five negative smears were encountered in 13 cases of preinvasive carcinoma of the cervix.

During the past five years in the Vincent Memorial Laboratory, 3710 cases have been studied by vaginal smear with a total diagnostic error of 2.8 per cent. Of 3327 cases without cancer, a mistaken positive diagnosis was made in 55. This represents an error (negative cases called positive) of 1.6 per cent.§

A recent publication suggests that many patients hitherto considered to have early cervical carcinoma, presenting but a short history of bleeding, or a minimal visible lesion may nevertheless be in an advanced stage of the disease, some even with metastases.[10] There is evidence that carcinoma of the cervix presents neither symptoms nor signs for as long as eight years after its inception.[11, 12] In 47 cases of preinvasive carcinoma of the cervix reported by Pund and Auerbach[10] only 1 out of 4 patients had abnormal bleeding, and the cancer was not recognizable to inspection in a single case. If the gynecologist cannot visualize any suspicious area, he must take a biopsy specimen (or three or four specimens) hit or miss; 25 per cent of such biopsies fail to include epithelium,[13] and a larger number fail to include the malignant area.

In the diagnosis of very early carcinoma of the cervix, the vaginal smear is not infrequently more accurate than the biopsy.

The following and similar cases demonstrate that preinvasive carcinoma is often more successfully diagnosed by cytologic than by histologic examination:

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§Of 285 cases of cervical cancer, 31 have been missed by smear; in 20 of 98 cases of endometrial carcinoma the smear was negative. It is evident that the vaginal smear is most accurate in cervical and less satisfactory in the diagnosis of fundus carcinoma.

A 49-year-old woman, 3 years after the menopause, was given estrogens because of arthralgia. After 3 months of estrogen therapy, bleeding for 1 day occurred. The cervix was normal to inspection. A vaginal smear was positive. Biopsies taken from three areas in the cervix showed chronic cervicitis. A complete hysterectomy was done. The cervix was grossly normal. However, after the cervix had been sectioned, carcinoma was found in an area not over 0.5 mm. in diameter.

A 42-year-old woman was admitted to the hospital because of a lump in the right breast, which proved to be benign. Pelvic examination showed a cervical erosion and leukoplakia. Cytologic examination of the vaginal secretion was positive for cancer. The diagnosis on a biopsy specimen was leukoplakia. A total hysterectomy was performed. Histological examination disclosed preinvasive carcinoma of the cervix.

Seventeen cases of preinvasive carcinoma of the cervix, in which vaginal smears were positive in 15, have recently been reported.[10] Of thirteen biopsies taken from these 17 patients histologic diagnosis on the initial biopsy was positive in only 5. Four patients had had no symptom; a neoplastic lesion was unsuspected and was discovered only by routine vaginal smear.

Cancer of the Lung

Because pulmonary neoplasms desquamate into the bronchial secretion, the sputum has been studied for possible carcinoma of the lung. Dudgeon[14] was the first to introduce wet fixation as a diagnostic method. Gowar,[15] Wandall[16] and others have obtained by this method a diagnostic accuracy of 60 to 80 per cent. Seed and Graham,[17] in our laboratory, have examined a single sputum specimen from each of 250 cases. A correct diagnosis for or against cancer was made in 73 per cent. In cases suspected of cancer the diagnostic error can be reduced by the examination of several specimens of sputum. It is important to note that in this series of 56 cases of primary pulmonary carcinoma, 7 cases were operable; sputums from 6 of these contained cancer cells.

Cancer of the Urinary Tract

A diagnosis of cancer of the urinary tract may be made by the examination of smears obtained from the urinary sediment. Our diagnostic accuracy has approximated 50 per cent. The following cases illustrate the value of the method:

I. M., a 60-year-old patient, complained of hematuria and acute retention. Cancer cells were found in the urinary sediment. Cystoscopy showed cystitis, but no evidence of neoplasm. A biopsy taken at that time revealed only chronic inflammation. A total cystectomy was performed. Histologic examination disclosed cancer of the bladder, Grade II-B.

A. S., a 79-year-old patient, had recurrent hematuria. Retrograde pyelograms showed a filling defect in the right kidney consistent with blood clot, but the possibility of tumor could not be excluded. The urinary sediment was positive for cancer. A nephrectomy was performed; cancer of the renal pelvis, Grade II-B, was found by the pathologist.

Until more statistical evidence is available, however, we believe that major operative procedures should not be undertaken on the basis of a positive cytologic diagnosis of the urinary sediment unconfirmed by other examinations.

Gastric Carcinoma

The early detection of cancer of the stomach has so far proved an almost insoluble problem to the surgeon. Between 10 and 20 per cent of lesions that later prove malignant continue to be diagnosed as benign. Diagnosis of lesions that are grossly benign but histologically malignant is impossible either by x-ray examination or by gastroscopy; moreover, the surgeon at the operating table is frequently unable to decide whether a given lesion is cancer or benign ulcer. Pack and Livingston[18] state: "If every patient with gastric cancer entered the best surgical clinic in the world, 95 per cent would remain uncured and approximately 90 per cent would be dead of the disease in 18 months." Without earlier diagnosis the salvage rate cannot be improved.

In 1946 Papanicolaou[2] reported 9 cases in which the aspirated gastric secretion was studied for cancer cells. Two of the patients had carcinoma. A cytologic diagnosis of cancer was made in both.

In the Vincent Memorial Laboratory gastric fluid in 50 cases has been examined. Twenty-four of these patients had cancer of the stomach. Cancer cells were recognized in the gastric secretion of 15. One case with a benign lesion was mistakenly called malignant. Cancer cells were found in 2 cases in which the excised stomach showed no gross evidence of neoplasia. Histologically both were diagnosed as preinvasive carcinoma. Of the 5 *early* cases of gastric carcinoma studied, cancer cells were found in the gastric fluid in 4. In 1 case, except for the cytologic report, cancer was totally unsuspected—preoperatively, at operation and on examination of the gross specimen. The application of cytologic examination to the diagnosis of early gastric cancer is now being investigated in the Vincent Memorial Laboratory.

Summary

The cytology of various body fluids has been studied as a means of cancer diagnosis. The value of the method for the diagnosis of uterine carcinoma has been established. In the detection of early cervical neoplasms, it is apparently more accurate than routine biopsy. Studies are in progress to determine the efficacy of cytologic examination in the diagnosis of cancer of the stomach, lung and urinary tract. In the early diagnosis of gastric carcinoma the new method may prove to be of great value.

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RECENT THERAPEUTIC TRENDS IN ALLERGY*

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BOSTON

TWO topics of current interest in allergy are considered in this study: the present status of histamine, with particular reference to the new antihistaminic drugs; and the role of inhalation therapy, including the aerosols.

It would be satisfactory to be able to report that recent advances in allergy have made clear an understanding of the fundamental characteristics of the allergic state. It is true that investigators are gradually learning more about the trigger mechanism that sets off the explosion, but unfortunately they are still ignorant of the nature of the charge with which the allergic gun is loaded. The chief constituent of this ammunition has long been supposed to be histamine. Study of this assumption has led to much investigative work over a period of years as well as to the development of several antihistaminic agents of clinical value. Feinberg[1] has reviewed this subject in an excellent article. A few points are worthy of emphasis, since they demonstrate the results of efforts to counteract the effects of this drug, whose role is presumed to be so important in the mechanism of the allergic reaction, particularly in the type associated with the immediate skin reaction and the production of edema and hyperemia.

As early as 1910, Dale and Laidlaw[2] called attention to the similarity of the action of histamine and the manifestations of anaphylactic shock in animals. In 1927 Best and his associates,[3] in demonstrating that histamine is normally present in many tissues, led the way to an explanation of its sources in the body. Variations in anaphylactic reactions in several species of animals were later considered to be due to varying concentrations of histamine in different organs.

In allergy in human beings, however, the importance of the role of histamine has not been so clearly shown, but has been inferred more from certain similarities observed between anaphylaxis in animals and allergic reactions in man and by the fact that histamine administered to man produces some if not all of the phenomena observed in clinical allergy. Investigation of the systemic effects of histamine led Weiss and his co-workers[4, 5] to observe that vital capacity was decreased and that attacks of wheezing were frequently produced in patients with asthma after the administration of histamine. Dautrebande et al.[6] further demonstrated the bronchoconstrictor properties of choline and histamine when employed as aerosols in human subjects. These observations were confirmed by Curry,[7] who pointed out that, whereas normal subjects showed no reduction in vital capacity after the administration of histamine, those with asthma did so if this drug was given by either the intramuscular or the intravenous route and, to a less extent, when it was administered under the tongue or by nebulization. Encouraging results have likewise been obtained by Curry[8] in a study of the effects of various drugs, including the antihistaminic agents, when he succeeded by their use in preventing or modifying changes in vital capacity after exposure to aerosolized extracts.

Treatment directed toward the histamine theory has taken several forms: immunization by treatment with histamine itself or histamine conjugate (hapamine); destruction by a ferment, such as histaminase; and inhibition or neutralization by the antihistaminic drugs.

Each of these methods of treatment has been tried. Desensitization by repeated injections of histamine has been widely attempted in allergic conditions in an effort to increase tolerance to this agent. The results of this type of therapy have been disappointing, and it is now concluded by most observers that such injections do not actually increase a subject's tolerance to histamine or significantly

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modify his own particular reaction to a given dose of this drug.

Histamine azoprotein, a histamine conjugate, has also been employed on the grounds that it might more readily stimulate antibodies than histamine

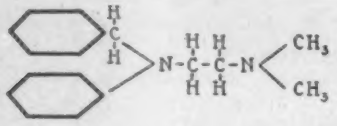

FIGURE 1. *(N'phenyl-N'benzyl-N-dimethylethylenediamine) Antergan.*

itself, but this has also failed to produce consistent enthusiasm.[1]

Histaminase provided what at first seemed a logical approach to a fundamental problem since this enzyme was proved capable of destroying histamine in many cases in vitro. In man, however, it did not produce comparable results so that even its discoverer, Best,[9] had to admit after ten years of trial that there was no physiologic basis on which to rest its clinical use.

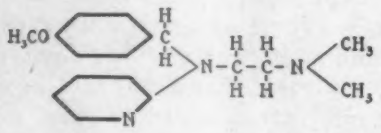

FIGURE 2. *(N-p-methoxybenzyl-N-dimethylaminoethyl α aminopyridine) Neoantergan.*

The development of the antihistaminic drugs constitutes the most recent and by far the most successful attack upon the effects of histamine. In contrast to attempted desensitization against histamine or its destruction by enzymic action, these drugs produce their effect by neutralizing histamine by competitive chemical action. It may also be mentioned as a matter of contrast, that epinephrine, ephedrine and the other sympathomimetic drugs act in an entirely different manner — namely, by vasoconstriction. This distinction is of particular clinical importance, since it means that both types of drugs may be used together without mutual interference.

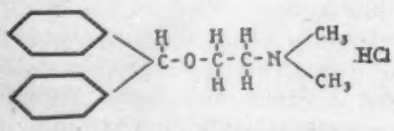

FIGURE 3. *(Beta-Dimethylaminoethyl Benzohydryl Ether Hydrochloride) Benadryl Hydrochloride.*

After extensive trials with various compounds that had been shown to possess histamine-inhibiting properties, experimental observations with two antihistaminic drugs were reported in France. Halpern,[10] described antergan in 1942, and Bovet and his associates[11] neoantergan in 1946. Both drugs are effective. The latter, which is less toxic than antergan, shows particular promise.

Benadryl and Pyribenzamine, the new American histamine antagonists, have had more extensive clinical trial than the French compounds and are now generally accepted as of proved value in the treatment of certain increasingly clearly defined manifestations of allergy.

The structural formulas of these four compounds show their close chemical similarity (Fig. 1-4).

Reports regarding the assets, liabilities and comparative merits and demerits of Benadryl and Pyribenzamine have flooded the literature. This paper is not concerned with summarizing these varying statistics but points out the conditions in which it is generally agreed that they are of value and to warn against their frequent side actions. Benadryl and Pyribenzamine are of greatest value in providing temporary relief in urticaria, angioedema and hay fever, in manifestations of serum disease, in the reactions due to penicillin or the sulfonamides and in the itching from atopic and contact dermatitis. They are less effective in perennial vasomotor rhinitis and even less so in asthma, particularly in cases of infectious or intrinsic etiology.

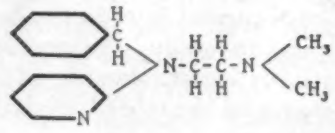

FIGURE 4. *(N'pyridil-N'benzyl-N-dimethylethylenediamine). Pyribenzamine.*

Side actions are frequent in both, the commonest of these being sedation and drowsiness. Vertigo, palpitation, nervousness, insomnia and gastric irritation appear less often. These occurrences sometimes become less marked after the first few doses, but they occasionally persist and necessitate discontinuance of the medication. The disadvantage of sedation may sometimes be converted to an asset when insomnia or anxiety complicates the picture, especially during the night or by day in cases of pruritus. Benzedrine may be of value in counteracting this drowsiness. There is a certain amount of selective response to these two antihistaminic agents in individual patients, both from the standpoint of therapeutic effect and in the appearance of side reactions.

An average dosage of 50 mg. of either drug after meals and at bedtime is commonly sufficient to con-

trol symptoms, but this must be varied both in time and amount of administration in accordance with the patient's tolerance. The daily dose may be increased to 400 mg. or over, in the absence of reactions, if necessary to obtain a clinical response.

It must be emphasized that these drugs do not immunize the patient, nor is their benefit more than a brief one, lasting but a few hours after each dose.[12] No evidence has been presented that they interfere with the mechanism of the production of immunity or that their prolonged and widespread administration is followed by remote toxic effects, but it is as yet too early for final judgment on these points.

The new antihistaminic agents are valuable adjuncts to the treatment of allergic disease, as epinephrine and ephedrine have been for some years. They do not minimize the importance of hyposensitization or of management by a carefully conceived and executed program, but when combined with other established methods of treatment, they do offer many allergic patients an increased chance of relief.

Inhalation therapy has made remarkable progress in recent years in the control of respiratory disease, including bronchial asthma. Various therapeutic agents and methods have been introduced, particularly by Barach,[13, 14] Segal[15] and others. The more notable advances have been the use of oxygen, mixtures of oxygen and helium and positive-pressure therapy, including the employment of therapeutic aerosols. Patients with severe asthma often respond to oxygen under normal pressure. If this fails, one should turn to oxygen or oxygen mixed with helium, preferably under positive pressure in both phases of respiration. The latter form of therapy can be administered with a Barach hood apparatus. If this is not obtainable, an O.E.M. mask, readily available to all physicians, may be used to supply positive pressure in the expiratory phase of respiration alone. Segal[15] recommends that positive-pressure therapy be carried on intermittently, for it may be tiring to the patient with uninterrupted administration, and he has further demonstrated that this form of therapy provides one of the most valuable methods in the treatment of severe bronchospasm.

Various therapeutic aerosols have been utilized for the management of certain phases of bronchial asthma. The bronchodilator drugs — epinephrine in a strength of 1:100 and vaponephrine and isuprel[16] (an isopropyl amino-ethanol) — have been found to be most effective for this purpose. A mixture of equal parts of 1 per cent Neo-Synephrin and any one of the above bronchodilators may occasionally prove of even greater value, since Neo-Synephrin, though a poor bronchodilator, is an effective bronchovasoconstrictor.

The necessity for an efficient nebulizer must be emphasized. It is essential that the average mass diameter of the aerosolized particles be in the neighborhood of 1 to 3 microns to ensure their transit into the lower respiratory passages and to prevent them from being deposited upon the mucous membranes of the upper respiratory tract. Most of the pioneer investigators in this field have found the vaponephrine nebulizer adequate for this purpose.[14, 15, 17, 18]

Antibiotic aerosols, particularly penicillin, have more recently proved of benefit in many respiratory diseases, such as lung abscess, bronchiectasis, acute laryngotracheobronchial edema and purulent sinus disease.

Numerous reports in the recent literature, both favorable and unfavorable, have presented over-all results of penicillin therapy in bronchial asthma by the intramuscular, oral and aerosol routes.[18–24] On the whole, these have been disappointing except in cases in which there has been complicating purulent infection. When such a condition has been treated in the sinuses, favorable results in a small series of cases have been reported by Barach and his associates[25, 26] with specially adapted equipment developed for the purpose. This consists of a negative-pressure sinus apparatus by which the nasal inhalation of penicillin aerosol is employed in conjunction with a scheme for interrupted negative pressure applied to the nasal passages. When this pressure returns to normal, penicillin is aspirated into the sinus cavities.

In the so-called "intrinsic cases" or in bacterial asthma, it might be thought that penicillin would often control the etiologic process and thereby arrest the disease, particularly when the drug can be concentrated locally in the pulmonary tissues, as penicillin aerosol can. In some cases, the penicillin-susceptible organisms can be eradicated in this way,[21] but the clinical course of the asthma is usually unaltered or is only temporarily improved. It should also be remembered that allergic reactions to penicillin, including the aerosol, are being encountered with increasing frequency, particularly in asthmatic subjects.[27–29]

Care must be exercised in the appraisal of the therapeutic efficacy of any procedure in bronchial asthma. The clinical picture may be modified by many factors other than the one under immediate consideration. Among these is the tendency for intrinsic asthma to exhibit seasonal fluctuations, improving in warm weather and becoming worse with recurrent infections in the winter. Hospitalization itself, with its change of environment, provides multiple factors of a therapeutic nature, both medicinal and psychologic, that often bring about a remission, as does the careful control of previously unrecognized extrinsic allergens or of structural abnormalities. Penicillin should therefore be considered as a therapeutic agent for the treatment of clear-cut infectious processes and not as a routine procedure in the therapy of bronchial asthma.

Brief mention should be made of promising results obtained after the recent employment of aero-

sols for the purpose of testing asthmatic patients who have failed to react to suspected pollens by routine skin tests. Lowell and Schiller[30] have exposed such patients to the inhalation of various pollen extracts, recording the resulting effect upon their vital capacities. These authors have been able to demonstrate that substances that produce a fall in vital capacity are of clinical significance as judged by the histories and by the production of mild asthma characteristic of the seasonal attacks.

Summary

The modern concepts of the possible role of histamine in the mechanism of the allergic reaction are discussed. It is pointed out that treatment with histamine or with histamine azoprotein does not give adequate clinical evidence of increased human tolerance to histamine and that the enzyme histaminase is not capable of destroying histamine in vivo. The new antihistaminic drugs, which apparently operate by competing with the liberated histamine in their attachment to the receptor cell, have been more successful in treatment. The temporary nature of their action, their advantages and their disadvantages are reviewed.

Recent advances in inhalation therapy for asthma are described, including the use of therapeutic gases, both with and without positive pressure, and the administration of various therapeutic aerosols. A new method is pointed out by which aerosolization may be utilized for further investigation of the action of drugs of potential value in allergy and for the study of cases of asthma of inhalant origin refractory to better known methods of testing. The limitations of penicillin in the treatment of chronic asthma are set forth.

Allergic symptoms are potentially recurrent and may appear in varying forms dependent upon the changing location of the shock organ. They are the manifestations of a chronic, constitutional inherited disorder, the exact nature of which is still unknown. No one method of therapy or agent that will afford more than temporary relief once these symptoms have appeared has yet been discovered, nor can it be instrumental in controlling the precipitating factors that lead to the appearance of manifestations recognized as allergic disease. For this reason it is strongly recommended that the new drugs and procedures outlined above, as well as all others that have been introduced to date, be employed, not as isolated methods of therapy but as supplementary aids to already well established principles of treatment. There is as yet no short cut and no substitute for sound allergic management, which includes prolonged observation and education of the patient in conjunction with elimination and desensitization when these procedures are indicated.

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SEPTICEMIA DUE TO *PROTEUS VULGARIS**

Review of the Literature and Report of a Case Cured by Streptomycin

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THE term *Proteus vulgaris* (*Bacillus proteus*) refers to a number of different species of a gram-negative, actively motile rod form originally described in 1895.[1] These organisms characteristically exhibit the "swarming" phenomenon in colonies on agar. They are widely distributed in contaminated soil and sewage and are found on the skin, in the urine and in the mouth.[2]

The Proteus organism was at first thought to be nonpathogenic, but Larson and Bell[3] established its pathogenicity for rabbits, rats and guinea pigs in 1915. It has since been implicated in a large number of pathologic states, though its usual status is that of a nonpathogen and it is found in a high percentage of normal stools.[4]

Proteus septicemia is a relatively rare condition. Cragg[5] stated in 1941 that 13 cases had been recorded in the literature. McKee[6] reviewed *P. vulgaris* infections in 1944 and found 23 cases of septicemia produced by foci of infection other than the genitourinary tract. Data on 52 reported cases[6–45] are presented below, together with a report of a case cured by streptomycin therapy.

AGE, SEX AND SOURCE

The youngest reported case was in a nine-day-old infant,[9] and the oldest in a seventy-five-year-old man.[30] Between these two extremes, the cases were distributed generally among all decades, with the exception that a larger proportion of cases were in the third decade. Of the patients who were under forty, roughly four fifths had middle-ear infection, and of those over forty, about four fifths had primary genitourinary-tract disease.

About 75 per cent of the patients were male and 25 per cent female.

Of 47 cases in which the source of the septicemia was established, 21, or 44.7 per cent, originated in the ear, nose or throat; 22, or 46.8 per cent, originated in the genitourinary tract, and 4, or 8.5 per cent, derived from miscellaneous foci.

Among the cases associated with genitourinary-tract infection, 7 followed directly the use of instrumentation (catheterization or cystoscopy) and 8 were caused by major operations of the genitourinary tract—5 after prostatectomy and 1 each after suprapubic cystostomy, nephrostomy and nephrolithotomy. Two cases were associated with pyelonephritis, and 1 each with cystitis, pyelitis, renal tuberculosis, carcinoma of the bladder and cord bladder.

The source of infection in the 21 cases involving the ear, nose and throat was the middle ear in 18, the tonsils in 2 and a questionable pharyngeal ulcer in 1 case.

The remaining 4 cases were associated with a suppurative ovarian cyst, a lung abscess, a war wound and meningitis in a nine-day-old infant.

PATHOLOGY

Few detailed pathological reports are available. Characteristically, all infected areas exhibited a foul-smelling, green or brownish-green pus. Lung abscesses containing the typical foul pus were found in 6 of 9 cases in which autopsy findings were reported. Isolated findings included septic thrombosis of the inferior vena cava, lateral sinus thrombosis, thrombophlebitis of the renal veins, congestion of the spleen, brain abscess, purulent meningitis from *P. vulgaris*, pyelonephritis, osteomyelitis and chronic otitis media. The microscopical pathology was not distinctive, an outpouring of polymorphonuclear leukocytes being most characteristic.

CLINICAL PICTURE

In most cases, the patients appeared acutely ill and ran a high, spiking fever with chills and a septic course. Occasionally a typhoidal type of fever curve was seen, and some cases diagnosed as typhoid fever came to post-mortem examination. Anemia was present in some cases, and leukocytosis in almost all. White-cell counts ranged from 8700 to 35,000, with an average level of 12,000 to 16,000. The differential count showed from 70 to 84 per cent neutrophils.

When recovery took place, the illness was usually of many weeks' duration. In cases in which operative procedures preceded infection, recovery, when it occurred, was more rapid.

Division of the cases into two groups based on the source of the infection — the ear and the genitourinary tract — establishes the symptomatology associated with most cases. In those deriving from the ear, a history of chronic otitis was almost invariable, and associated pain and discharge were present. In those related to the genitourinary tract, the history of previous operative procedures was present in 15 of 22 cases, and typical symptoms of urinary-tract disease with concomitant chills and fever were noted.

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Prognosis

In 48 cases in which the subsequent course was described, 31 patients, or 64.6 per cent, died, and 17 patients, or 35.4 per cent, recovered. The prognosis was far better in the cases deriving from the genitourinary tract than in those deriving from the ear, nose and throat. In the former group, the mortality was 36.8 per cent, whereas in the latter group it was 80.1 per cent.

Diagnosis

The diagnosis can be established only by obtaining a positive blood culture for *P. vulgaris*. When positive blood cultures are obtained, investigation of the two main foci of infection is imperative.

Case Report

A 44-year-old man entered the hospital with a chief complaint of chills and fever of 3 weeks' duration.

He had previously been admitted to the hospital seven times since 1932 for recurrent renal calculi, but on each occasion he had been able to pass the stones without operative intervention. The last previous admission had occurred 5 months before the present illness. At that time, the patient passed eight small calculi and one large calculus. After cystoscopy, he developed a shaking chill and fever, and during the week following discharge from the hospital, he had three episodes of chills and fever. One month after discharge, he began to notice moderate shortness of breath on exertion and at that time was told that he had a heart murmur. Three weeks before the present admission, he began to have recurrent episodes of shaking chills and fever at about 9 o'clock each evening. He was placed on sulfonamides and remained afebrile for a few days, only to have a recurrence of the chills and fever. Sulfonamides were discontinued, and penicillin therapy initiated, but the penicillin failed to influence the course. The patient was then hospitalized.

Physical examination revealed the presence of marked generalized pallor, slight cardiac enlargement, and a loud, harsh, apical systolic murmur heard throughout systole and masking the first sound. No other positive physical findings of note were observed.

On the afternoon of admission, the temperature was normal, but it rose to 103°F. in the evening, after a shaking chill.

Examination of the blood showed a hemoglobin of 9 gm. and a white-cell count of 10,000 to 12,000, with 74 per cent neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The hematocrit was 28 per cent, and the corrected sedimentation rate 30 mm. in 1 hour (Wintrobe method). The blood sugar was 109 mg., and the blood urea nitrogen 22.1 mg. per 100 cc. The total protein was 7.5 gm. per 100 cc., with an albumin of 4.1 gm. and a globulin of 3.4 gm. The icteric index was 6.0; the blood calcium was 10.6 mg. and the phosphorus 3.5 mg. per 100 cc., and the alkaline phosphatase 4.5 units per 100 cc. The urine had a specific gravity of 1.024 and contained a trace of albumin, with 10 white cells per high-power field in the sediment and a negative Sulkowitch test.

Blood cultures were taken, and on the 6th day after admission, a pure culture of *P. vulgaris* (15 colonies per cubic centimeter) was reported. At the same time, a pure culture was found in the urine. Positive blood cultures were again obtained during the next 2 days, and the patient was then placed on streptomycin, 0.3 gm. every 3 hours. He remained on streptomycin for 10 days, receiving a total of 25 gm. No positive blood or urine cultures were obtained after the initiation of streptomycin therapy. After the 1st day of treatment, the patient had no more chills, and the temperature never went above 101°F. After a week of normal temperature, he was discharged and has remained well ever since.

Discussion

From the review of the literature presented above, it is apparent that Proteus septicemia formerly had a high mortality. That the prognosis was worse in cases associated with disease of the ear, nose and throat was probably due to the long-standing and deep-seated infection that led up to the septicemia.

Therapy, until the advent of streptomycin, was varied and not demonstrably the direct cause of cure. Surgery was utilized in 9 patients. Of 6 patients on whom mastoidectomy was performed, all died. Two of 3 patients on whom nephrectomy was performed survived. Recovery followed bacteriophage in 1 case[40] and vaccine in 2 cases,[10, 13] and sodium ricinoleate therapy was followed by recovery in 1 case.[40] Sulfonamides were used in 3 cases; 2 of the patients died,[43, 44] and 1 survived.[6]

In the National Research Council Report on streptomycin[46] 5 cases successfully treated with streptomycin were noted. No data were obtainable in these cases. The case presented above illustrates further the striking effect of streptomycin on the Proteus organism. This effect has been demonstrated experimentally in the chick embryo,[47] and in disease of the genitourinary tract, good therapeutic results have been obtained.[48] Thus, a sharp reduction in the hitherto high mortality may be expected in the future.

Summary

Data on 52 cases of septicemia due to *Proteus vulgaris* reported in the literature are presented. These cases fell into two main groups: those associated with genitourinary-tract disease, and those associated with infection of the ear, nose and throat. Until the advent of streptomycin, the prognosis in these cases was poor.

A case cured by streptomycin is presented, and it is suggested that a striking reduction in mortality may be expected.

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MEDICAL PROGRESS

EPIDEMIOLOGY OF TULAREMIA IN MASSACHUSETTS WITH A REVIEW OF THE LITERATURE

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ALTHOUGH tularemia is considered a "truly American disease," Ohara[1] refers briefly to a historical account of a disease that he thinks was tularemia, described in 1837 by a Japanese physician, K. K. Homma.[2] Ohara states that Homma, under the heading of intoxication of rabbit meat, described in detail the incubation period and symptoms of a disease that, according to Homma, had not theretofore been described. After tularemia became known in America, physicians in the West claimed to have seen similar cases as early as 1907 in Arizona and 1909 in Missouri.

In 1911 McCoy[3] contributed the first information of the etiology of this disease by his discovery of what he called "plague-like disease of rodents" prevalent among the California ground squirrels, first observed in squirrels received from Tulare County, California. McCoy and Chapin,[4, 5] in 1912, discovered the causative organism of the disease in the California ground squirrels and named it *Bacterium tularense*,‡ after Tulare County. McCoy and Chapin,[4, 5] in 1912, also reported complement fixation and agglutination of *Bact. tularense* by the serum of Chapin and a laboratory attendant, both of whom were extensively engaged in handling or dissecting infected rodents in the San Francisco laboratory and constituted the first cases of laboratory infection in man.

In Utah a disease of man was for several years popularly known as "deer-fly fever," owing to the belief that the infection was caused by the bite of the bloodsucking fly, *Chrysops discalis*, commonly found on horses. This belief found expression in a paper read before the Utah State Medical Association, Salt Lake City, on October 3, 1910, by

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‡Now more technically called *Pasteurella tularensis.*

Pearse,[6] of Brigham City, Utah. Pearse's cases constitute the first reported human cases of tularemia differentiated clinically, although the disease was not demonstrated to be tularemia until 1919.

Vail,[7] Sattler[8] and Lamb,[9] three ophthalmic surgeons of Cincinnati, Ohio, each reported a case of "conjunctivitis tularensis" in 1914, 1915 and 1917, respectively, in persons who had dressed rabbits and in whom the seat of primary localization was the conjunctival sac. The bacteriologic diagnosis of these 3 cases was made by Wherry and Lamb,[10] who isolated *Bact. tularense* on a culture medium from guinea pigs into which the eye scrapings had been injected. Vail's case is the first human case of tularemia on record to be diagnosed bacteriologically. Wherry and Lamb[11, 12] also isolated the organism from two wild cottontail rabbits found dead and collected in southern Indiana near the residence of Sattler's patient. This isolation from wild rabbits was the first bacteriologic proof of the rabbit reservoir of infection.

Francis,[13, 14] investigating "deer-fly fever" in Utah in 1919, recognized the identity of the Utah disease among human beings and the California ground-squirrel disease, and named the disease tularemia on account of the presence in the blood of the causative organism. He furnished proof of this identity by isolating *Bact. tularense* from 7 fly-bitten human patients, from 17 wild jack rabbits and from a ground squirrel, by demonstrating anti-tularense agglutinins in his own blood and that of his assistant, both of whom had contracted the disease in the field laboratory, and by transmitting the infection among laboratory animals by the deer-fly, *Chrysops discalis*.[15]

Parker, Spencer and Francis,[16] of the United States Public Health Service, in the course of their studies of Rocky Mountain spotted fever at Hamilton, Montana, recognized the agency of the common wood tick of Montana, *Dermacentor andersoni*, as a host and transmitter of tularemia.

Dr. J. Lawn Thompson,[17] of Washington, D. C., was the first to recognize a case of tularemia in the eastern United States when he made the diagnosis in a market man who was engaged in skinning and dressing wild rabbits in the Washington market in November and December, 1921. Francis[18] isolated virulent *Bact. tularense* from seven of 914 rabbit livers examined in the Washington, D. C., market in January, 1923.

Four articles in Japanese text, dealing with a disease of man occurring in Japan, were proved by Francis and Moore[19] to have been tularemia, although none of the articles contained specific mention of tularemia or of the published work of the American investigators on the disease. Two of these articles were by Ohara,[1, 20] one by Aoki, Kondo and Tazawa,[21] and one by Iwamoto, Muto and Aomura.[22] The dates of publication were between March 12, 1925, and July 10, 1925. Proof of the identity of the American and Japanese diseases was furnished by Moore and Francis,[19, 23] who, on seeing Ohara's first descriptions, requested material from Ohara and demonstrated complete serologic and bacteriologic proof of the identity of the Japanese disease and tularemia of the United States.

Since the original discovery by McCoy in 1911, tularemia as an endemic disease of man has been observed in the forty-eight states, the District of Columbia and Alaska; it has been reported from Canada, Japan and the Soviet Union and, in recent years, in epidemic proportions from Europe (Sweden, Norway, Bohemia, Austria, Turkey and Germany).

Modes of Transmission

Tularemia is primarily a disease of certain rabbit-like mammals (Order *Lagomorpha*) and occasionally of certain rodents (Order *Rodentia*) and other wild mammals (shrew, opossum, beaver, coyote, red fox, gray fox and so forth) and game birds (sage hen, quail and grouse). A recently published list of vertebrates known to be naturally infected with tularemia includes, for the United States and Canada, six species of birds and twenty-eight species of mammals.[24] Although the disease is readily transmissible to man, human infections are only accidental. After recovery, one attack confers lifelong immunity.

Contact

Human infections may be acquired from three main sources[25] the most common method, in eastern North America particularly, being by contact with a diseased animal. The bacteria may enter the human skin, which may be abraded or possibly even intact, or the mucous membrane (particularly that of the eyes) during the skinning and dressing of infected wild animals or while their skins are being handled. Thorough cooking kills the organism; however, infection may occur from eating raw or improperly cooked infected meat.[26] The disease has been known to be conveyed to people by the bite or the scratch of some infected animals. Self-inoculation by contact is prevalent among hunters, cooks and butchers, and there are often cases in large cities in which so-called "market fever" is well known among marketmen. Infection by contact is most frequent from November to January, during the hunting season, when cottontail rabbits, particularly, are for sale. Dogs and cats are susceptible, and have been known to contract the disease by eating raw meat of sick wild rabbits. In dogs, *Bact. tularense* may persist for many days without any outward symptoms.[27] Although the domestic rabbit is susceptible to experimental tularemia, rabbits raised in rabbitries have very rarely been found infected in this country and therefore may be handled and eaten with safety.[28, 29]

Ticks

Tularemia is usually transmitted among wild mammals and birds by infected ticks, either by the bite or, more probably, by the feces that the ticks void while engorging on the host. Several species of ticks are known as natural or potential vectors. The rabbit tick, *Haemaphysalis leporis-palustris*, one of the most common ticks, has been found infected in nature[30] and transmits the disease in the laboratory.[31] Infected female ticks also pass on the bacterium to their eggs and larvae.[32] *H. leporis-palustris* is a particularly active transmitter, since all stages — larvae, nymphs and adults — occur often in unbelievable numbers on wild *Lagomorpha*, the adults being restricted to this type of host. Larvae and nymphs, however, often attach themselves also to migratory game birds, which may thus carry infected ticks over long distances and into new territory. It seems probable that *Bact. tularense* survive the winter chiefly in infected *H. leporis-palustris*, which have been dropped off from infected cottontail rabbits dying of the disease.[33] All stages of this tick hibernate away from the host. The rabbit tick is not known to attack man and, therefore, is not instrumental in the transmission of tularemia from infected animals to human beings. The Rocky Mountain wood tick, *D. venustus* (Banks)* is infected in nature in Montana.[16,30] It has also been proved that this tick is a true biologic host of *Bact. tularense*, which it harbors not only in its feces but also in the epithelial cells of the digestive tract and malpighian tubes and in the celomic fluid. Furthermore, an infected female *D. venustus* will transmit *Bact. tularense* to a certain percentage of its eggs, larvae and nymphs.[34] The presence of tularemia in the Pacific coast wood tick, *D. occidentalis* Curtice, was demonstrated in California.[35] The eastern wood tick, *D. variabilis*, was found infected with the disease in nature, notably in Minnesota, by Green.[36] According to Philip and Jellison,[37] in this tick the bacteria may also be transmitted by an infected female to part of the progeny, through the eggs. However, in later investigations by Bell[38] no hereditary infection could be obtained, and it was concluded that such transmission appears to be of no significance for *D. variabilis*. Bell pointed out that the lack of difficulty of hereditary infection of the tick may be a most important limiting factor in the epizootic course of tularemia. He also demonstrated that infected *D. variabilis* feeding on immune or normal hosts lose their infection, presumably owing to the stimulating effect of the blood meal upon a normal bacteriocidal function of the ticks' gut. Before losing their infection as a result of feeding, such infected ticks may nevertheless inoculate a normal host, which will later on be a source of infection to other ticks feeding upon it. On the other hand, when fed upon an immune host, infected ticks will not infect it, so that such an animal will not transmit the disease further to clean ticks. The number of animals that have become immune by a previous mild or chronic infection in a given area may also be of importance in limiting the spread of tularemia.

Wild rabbits and hares and their ticks are one of the most serious health problems, these animals being often infected with tularemia. Because many of them are handled by hunters, farmers, marketmen and consumers, they are a main source of human infection. All *Lagomorpha* are susceptible to the disease.[29] The snowshoe hare (*Lepus americanus*), the jack rabbit (races of *Lepus californicus*) and the cottontail rabbit (*Sylvilagus floridanus*) have all been found infected in nature. Among the *Lagomorpha*, tularemia is transmitted almost exclusively by *H. leporis-palustris*; rabbits and hares are the only efficient breeding host of this tick. The extent to which the larvae and nymphs of *D. variabilis* infect rabbits and hares in eastern North America is imperfectly known; however, some rodents, particularly the meadow mouse (*Microtus pennsylvanicus*), are the chief hosts of the larvae and nymphs of *D. variabilis*. The abundance of meadow mice is often closely correlated with the prevalence of *D. variabilis* in a given locality, such as the Cape Cod area and the neighboring islands. Little is known, as yet, concerning the natural occurrence of tick-borne diseases in the northeastern United States.

In the northeastern United States some human cases seem to have been caused by the adults of *D. variabilis*, which must have become infected in the immature stages, on wild life, but tick-borne infection of man is possible only when wood ticks are active, particularly from March to August.

Other Bloodsucking Insects

The third method of transmission involves a variety of bloodsucking insects, such as the squirrel flea (*Ceratophyllus montanus*), the rabbit louse (*Haemodipsus ventricosus*), the squirrel louse (*Neohaematopinus laevusculius*), two western species of deer flies (*Chrysops discalis* and *C. noctifer*), some western species of horseflies (*Tabanus*), the stable fly (*Stomoxys calcitrans*), a species of the black fly (*Simulium katmai*) and several species of mosquitoes (*Aedes aegypti*, *Aedes cinereus* and others). With all these insects, transmission has been effected under laboratory conditions from sick to healthy animals, either mechanically by the bite (interrupted feeding) or by the feces.[32, 39] Such experiments do not, however, necessarily incriminate these insects as effective transmitters of the disease under natural conditions. In the northeastern United States, although several species of *Chrysops* are abundant and often attack people during the summer, they have been seldom incriminated in human cases of tularemia.

*The same species as *D. andersoni* (Stiles).

Ingestion of Food and Water

In recent years, a fourth possible source of infection has come to light — namely, drinking water contaminated by infected animals, particularly muskrats and beavers.[40–42] Schuller and Erdman[43] describe an epidemic occurring in Germany during the summer of 1942, when 100 cases of tularemia were ascribed to the Dnieper River water and food in the township of Tchirin contaminated by mouse and rat excreta. Khatenever,[44] in 1943, described an epidemic in Russia in which many patients were infected through eating and drinking material contaminated by infected field and house mice.

Randerath[45] makes a reference to the origin of an outbreak among human beings during the winter of 1942–1943 on the eastern German front, where there had been an increase the previous autumn in field mice that had become infected from water rats. When, at the onset of cold weather, the troops were housed, they came into contact with the mice, and cases of tularemia occurred. He believed that food and water may have been the vehicles of transmission.

Inhalation

Another source of infection recently uncovered is inhalation. Maisky,[46] in 1945, wrote of epidemics occurring in central Russia that were due to threshing ricks contaminated by infected rodents. Infection occurred by the inhalation of dust, giving rise to the typhoidal and pneumonic forms of the disease. Similar epidemics are described by other Russian writers.[44, 47]

Tularemia in Massachusetts

Prior to 1937 only 3 cases of tularemia in human beings were reported in Massachusetts, and it was definitely ascertained that these infections had their origin outside the Commonwealth. However, in 1937 the first case of human tularemia definitely contracted in the Commonwealth was reported from Falmouth. Since that time a total of 14 cases have been reported, 6 of these occurring in the last two years. Furthermore, 8, or 57.2 per cent, of the cases have occurred on Cape Cod, 3 more, or 21.4 per cent in Plymouth County, which is adjacent to Cape Cod, and the remaining three, or 21.3 per cent, in the eastern part of the Commonwealth (Waltham, Georgetown or Amesbury and Boston). The ages varied from three to sixty-eight years, 6 female and 8 male patients being afflicted. All patients recovered except 1 man (Table 1, Case 13), who died nine months after contracting the disease. The type of disease varied, 7 patients having the ulceroglandular type 4 the pneumonic, 2 both ulceroglandular and

Table 1. *Cases of Tularemia Reported in Massachusetts from 1929 to 1947.*

Case No.	Age	Sex	Locale	Time	Method of Transmission	Incubation Period	Type of Lesion	Laboratory Confirmation
	yr.					*days*		
1	48	M	Boston[48]	December, 1929	Skinning of rabbit from Illinois	3	Ulceroglandular (right index finger and arm)	Agglutination 1:640
2	—	M	Cumberland Island (off Florida)[49]	March, 1929	Wood tick or deer fly	?	Ulceroglandular	Agglutination 1:1280
3	32	M	Colorado	May, 1934	Handling or eating of wild rabbit	4	Glandular (? septicemic and pneumonic)	Agglutination 1:1280; Foshay skin test positive.
4	10	F	Falmouth[50]	June, 1937	Dog (killing or eating wild rabbit, became ill 3 days after patient)		Typhoidal	Agglutination 1:1280; agglutination test on dog 1:40.
5	6	F	Falmouth	June, 1938	Tick bite	1–5	Ulceroglandular (postauricular region)	—
6	48	F	Falmouth[51]	July, 1939	Tick bite	1–7	Ulceroglandular (posterior aspect of left thigh)	Agglutination 1:1280; Foshay skin test positive.
7	38	M	Georgetown or Amesbury	November, 1941	Patient shot and skinned a wild rabbit	?	Ulceroglandular (right index finger and arm)	Agglutination 1:640
8	38	F	Falmouth	June, 1943	Tick bite	7	Pneumonic	Agglutination positive
9	38	M	Falmouth	August, 1943	? Tick bite, 6 weeks after case in wife (Case 8)	?	Pneumonic	Agglutination: blood, 1:320; pleural fluid, 1:1280; *P. tularensis* isolated from pleural fluid.
10	52	M	Waltham	May, 1943	Insect bite (? tick)	3	Ulceroglandular (anterior aspect of thorax)	Agglutination 1:320
11	13	M	Scituate	November, 1944	Patient killed and skinned a wild rabbit	?	Ulceroglandular	—
12	11	M	Martha's Vineyard	August, 1946	Tick expelled from suppurating left supraclavicular abscess	?	Ulceroglandular (left eye and supraclavicular area)	Agglutination 1:1280
13	64	M	Boston	October, 1946	Contact (? vector) chef in restaurant	?	Pneumonic — ulceroglandular (left thumb)	Agglutination 1:1280
14	3	M	Bourne	June, 1947	Tick bite (on forehead)	?	Ulceroglandular	Agglutination 1:2560
15	58	F	Bourne	June, 1947	Tick bite	1	Ulceroglandular (left scapular region)	Agglutination 1:2560
16	68	M	Duxbury	June, 1947	Tick bite (on left leg)	?	Pneumonic	Agglutination 1:2560
17	—	F	Wareham	July, 1947	Tick bite (on scalp)	7–14	Pneumonic	Agglutination 1:1280

pneumonic, and 1 typhoidal. The diagnoses were confirmed by positive agglutination tests, which showed a maximum rise in titer, on the average, by the third week varying from 1:320 to 1:2560 in all but 2 of the cases. In 1 case (Table 1, Case 9), *Bact. tularense* was isolated from the pleural fluid after passage through guinea pigs and mice. The incubation period on the average was within seven days of exposure.

It is interesting to note that 8, or 57.2 per cent, of the patients were definitely ascertained to have been bitten by ticks, and 2 were probably bitten by ticks. Contact with rabbits was definitely established in 2 cases; contact with a dog that was infested with ticks and later manifested a positive agglutination for tularemia, with a titer of 1:40, was responsible for another case (Table 1, Case 4). In another case (Case 13) the source of infection could not be ascertained, except that it was probably by contact because the illness began with an infection of the thumb, pulmonic involvement eventually occurring. Furthermore, the patient worked as a chef in a restaurant, handling all sorts of meat but denying exposure to rabbits or rabbit meat.

Of the 8 patients infected by ticks, 5 lived on Cape Cod, 1 on Martha's Vineyard, and 2 in Plymouth County. Of the 2 probably infected by tick bites, 1 was located on Cape Cod and 1 in Waltham (metropolitan Boston). The case resulting from contact with an infected dog occurred on Cape Cod also. The 2 cases due to contact with rabbits occurred in Plymouth and Essex counties respectively.

The Tick Problem

The south side of Cape Cod and the islands to the south — Martha's Vineyard, Nantucket and Naushon — are heavily infested. Ticks are less abundant on the north than on the south side of the Cape, and there are few to be found north of Plymouth, or inland beyond Middleboro and Taunton. Along the coast there is a marked diminution from Marion westward.[52] *D. variabilis* (wood or dog tick), *H. leporis-palustris* (rabbit tick), and *Ixodes dentatus* are the most prevalent; however, *I. scapularis* (black-legged tick), *I. muris*, *I. marxi*, *I. cookei*, *I. brunneus* and *H. chordeilis* are also abundant.

The larvae and nymphs of *D. variabilis* engorge preferably on small rodents, which are the true breeding hosts of the immature instars. A few of these sometimes stray onto rabbits, larger mammals or birds, but it is questionable whether they are capable of moulting after engorging on these unusual hosts. The meadow mouse, *Microtus p. pennsylvanicus*, is the preferred host of larvae and nymphs in the Cape Cod area. Most adult forms attach to and engorge on large and medium-sized mammals, the domestic dog being the favorite host. Man is readily attached to, but is only an accidental or stray host and not important to the survival of the species. In the Cape Cod area, adult ticks appear and are active from the latter part of April to the end of August.

The normal breeding hosts of adult and early stages of *H. leporis-palustris* are several species of hares and wild rabbits. Although this is the most important vector of tularemia in nature among rabbits and hares, it rarely bites human beings (as mentioned above); however, its larvae and nymphs are occasionally found on cats and dogs. Herman,[53] in 1938, found 18 out of 31 song sparrows infested with this tick on Cape Cod so that it can be distributed by the migration of birds.

I. dentatus appears to be a specific parasite of the *Lagomorpha* (rabbits and hares) at all stages,[54] but immature stages are sometimes found on rodents and birds. The normal hosts of the immature stages of *I. scapularis* are small mammals, particularly the white-footed mouse, but the adults attack a variety of large and medium-sized mammals straying occasionally onto man. *I. muris* appears to be at all stages a frequent parasite of small rodents, particularly the field mouse; occasionally, it attacks small migratory birds. *I. marxi* occurs normally on chipmunks and squirrels, and *I. cookei* infests medium-sized mammals, particularly *Carnivora*. *I. brunneus* and *H. chordeilis* are specific to birds. It is not yet known what part, if any, these ticks play in the transmission of tularemia.

It is readily conceivable how tularemia could be spread through the tick family and wild life once the infection has been introduced into a tick-infested area such as Cape Cod. *H. leporis-palustris* and *I. dentatus* could spread the disease from rabbit to rabbit, the former transmitting it to birds and the latter to field mice also. *I. brunneus* and *H. chordeilis* could spread it from bird to bird and *I. scapularis* and *I. muris* from mouse to mouse. In such a way a vicious circle could be formed, increasing the danger to man.

The Rabbit Problem

Prior to 1937 no rabbits were imported privately from the West; however, 26,290 Western rabbits were liberated in Massachusetts in that year and up to and including 1940. Of these, 788 were released in the tick-infested counties of southeastern Massachusetts. The first case of tularemia appeared in Falmouth in June, 1937, whereas, the first shipment released in that area was in March, 1937. From then on, cases have appeared regularly in the area of high tick prevalence. It is interesting to note that all the cases occurring on Cape Cod have been on the south shore.

In March, 1941, a shipment of cottontail rabbits was released in the vicinity of Lawrence, Massachusetts, and in November of that year a case of

tularemia was reported from that area, resulting from the skinning of wild rabbits shot in hunting.

In 1940, at the request of the Division of Fisheries and Game of the Massachusetts Department of Conservation, Belding and Merrill[85] examined post mortem 136 rabbits that had been imported by Massachusetts game clubs and had died in transit or shortly after their arrival in Massachusetts. Two of these rabbits were found to have tularemia. A previous series, in 1937, revealed no infection in 194 imported rabbits; therefore, the prevalence of tularemia in 2 out of 330 rabbits (0.6 per cent) was taken to correspond closely with the usually accepted incidence of 1 per cent infection among wild rabbits. The 2 tularemic rabbits were found in the shipments coming from Missouri and Arkansas (states with a total of 583 and 322 human cases reported for the period extending from 1937–1940).

The imported rabbits were admitted to Massachusetts under certification by accredited health authorities at the shipping points. The certificates stated that there had been no epidemic of tularemia or rabbit fever in the last two years in the counties in which the rabbits were trapped, and that these counties were free from contagious and infectious rabbit diseases. The presence of tularemia in certified rabbits from two states indicates that such guarantees are inadequate to prevent the inclusion of tularemic rabbits in these shipments.

Although there were no importations from 1942 to 1945, 4 cases of tularemia were reported during this period (2 from Cape Cod, 1 from Plymouth County, and 1 from Waltham). Three of these cases were ascribed to ticks, and 1 to contact with wild rabbits.

During 1946 approximately 3000 wild rabbits were again imported, mostly from Arkansas and Kansas, into Massachusetts by game clubs. Although none were released on Cape Cod, some were released in Bristol and Plymouth counties. During 1946 a case of tularemia was reported from Martha's Vineyard, and another from Boston. However, in 1947 there were 2 cases in Bourne (Cape Cod), and 2 in Plymouth County.

Discussion

From the material presented above, it appears that tularemia did not exist in Massachusetts prior to 1937. Although the medical profession had known about the disease since 1911, no cases except the 3 contracted outside the Commonwealth were reported prior to that year. In the spring of 1937 the first importations of wild rabbits from the midwestern states began, and the first case of tularemia definitely contracted in Massachusetts was reported during the following summer from the tick-infested area of the Commonwealth.

The fact that these wild rabbits were imported from areas where tularemia was prevalent and that some were proved to be infected with tularemia, in spite of certification from the exporting areas, leads one to believe that the disease was introduced into Massachusetts by this means.

Although these wild rabbits were released throughout the Commonwealth, only the tick-infested regions of Cape Cod and Plymouth County have persistently reported sporadic cases of tularemia because of the prevalence of ticks to maintain the focus. Fortunately, although ticks can spread and maintain a focus, there have been no outbreaks of any consequence in Massachusetts. This may be due to certain factors, as yet not fully known, limiting the spread of infection, even though the reservoirs and vectors are present in variable numbers. However, since there has been a regular occurrence of cases of tularemia in the tick-infested areas from 1937, one can assume that there is a small endemic focus in Massachusetts. The future of this focus cannot be predicted so far as its maintenance is concerned; however, its spread can be prevented by control of the tick population and by the placing of definite restrictions upon the introduction of fresh animal hosts and possible reservoirs such as wild rabbits.

The control of the tick population can be approached in several ways, none of which are very satisfactory in the ultimate eradication. Destruction with insecticides such as nicotine sulfate, sodium fluoride and DDT solutions is of value only on a very limited scale. Destruction of wild animal hosts as a means of eliminating the ticks from a given area seems an impossible task, for the arachnids are numerous and varied among both mammals and birds. The use of insect parasites such as the chalcid flies, if they became well established, could conceivably do much to reduce the tick population by killing a percentage of the nymphs. However, the two known chalcid parasites of ticks (*H. hookeri* and *I. caucurtei*) do not seem to be particularly attracted by *D. variabilis*; hence, their introduction is hardly an effective control measure for this tick.

Individual protective measures against ticks by man can be the most important factor in the avoidance of tularemic infections. Walking in woods and pastures should be avoided as much as possible during the tick season; if such walks are unavoidable, adequate clothing covering as much of the body as possible should be worn. Upon return from a heavily infested area, clothing should be removed and treated with some insecticide, and the body searched for any attached ticks. Particular care should be taken not to crush the ticks when removing them, since the infection can be acquired in this way. Ticks should also be removed from all household pets such as dogs before they are allowed to enter the house.

It has been shown that certification by authorities of exporting areas is inadequate in the prevention of the exportation of infected animals. Neither is the inspection of shipments at the point of release satis-

factory, for the disease is too easily overlooked in the gross. Guinea-pig inoculations have been demonstrated to be the only sure method of diagnosis and identification, but this is expensive and impractical because it is applicable only to dead rabbits. Inasmuch as tularemia exists in practically all states exporting rabbits, the best safeguard against the introduction and spread of tularemia in Massachusetts seems to be the banning of the importation of cottontail rabbits from the West.

Summary

The history of tularemia is discussed, beginning with a description of a disease with a similar symptom complex by Homma in 1837 and including the monumental work by various men of the United States Public Health Service, who established the disease as a definite entity with specific causal relations.

The following modes of transmission are presented whereby man is infected: by contact with infected wild animals; by ticks; by bloodsucking insects; by ingestion of contaminated food and water; and by inhalation.

The reported incidence of tularemia in Massachusetts consists of 14 cases occurring in ten years, with 78.7 per cent occurring in the southeastern sector (Cape Cod and Plymouth County area); 57.2 per cent were due to tick bites, 14.3 per cent were probably due to tick bites, 14.3 per cent were due to contact with infected rabbits, 7.1 per cent were due to contact with an infected dog and 7.1 per cent were due to contact with unknown sources.

Ticks capable of transmitting tularemia, particularly *Dermacenter variabilis*, *Haemaphysalis leporis-palustris* and *Ixodes dentatus*, are most prevalent on the south side of Cape Cod and islands to the south, with diminishing numbers in Plymouth County and northward.

The appearance of tularemia in Massachusetts coincides with the beginning of importations of wild rabbits from midwestern states where tularemia is prevalent, and their release in the tick infested area of the Commonwealth. The existence of tularemia in these imported rabbits was proved in 1940, and a 1 per cent incidence was calculated.

Satisfactory means of controlling the tick population have not yet been devised. Personal prophylaxis against ticks is very important in the avoidance of infection.

Certification of imported wild rabbits is inadequate in the prevention of the introduction of tularemia into a previously tick-free state.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 34061

PRESENTATION OF CASE

A twenty-six-year-old married woman entered the hospital complaining of abdominal pain.

Two days before admission she began having generalized, crampy abdominal pain. She had a small bowel movement that day. On the following day she was unrelieved following a good bowel movement. She experienced some anorexia, but no nausea or vomiting. On the day of admission, the pain moved to the right lower quadrant and became steady. Examination of the blood by a physician showed a white-cell count of 12,000 and hospitalization was advised.

The patient was believed to be pregnant, her last period having occurred just two months previously. Her appetite had been "picky" for a month.

Examination showed tenderness and only slight spasm at McBurney's point, with cough and rebound tenderness. Rectal examination disclosed a tender right vault, high up, and a normal left vault. The cervix was tender to motion. The uterus was enlarged and consistent with a two months' pregnancy.

The temperature was 98.6°F., the pulse 82, and the respirations 20. The blood pressure was 125 systolic, 70 diastolic.

Urinalysis was negative.

Immediately following admission, preoperative medication was given and operation performed.

DIFFERENTIAL DIAGNOSIS

DR. GORDON SCANNELL: I assume that the enlarged uterus, in addition to the missed period, was the reason for thinking that this patient was pregnant. I should like to know if she had had children, because if she had been pregnant before and thought that she was pregnant, she was probably right. If she had not had children I should like to know how long she had been married.

DR. MARSHALL K. BARTLETT: This was her second pregnancy. She was seen by an obstetrician on the day of admission. He thought that she had a normal two months' pregnancy.

DR. SCANNELL: In summary, this was a young married woman with a short history representing an acute surgical condition of the abdomen. We will therefore, on the date given, rule out chronic diseases and focus our attention on the immediate problem as it faced the surgeon on the night of admission. The symptoms were referable to the lower part of the abdomen and pelvis; there were definite signs of peritoneal irritation — namely, slight spasm at McBurney's point, and cough and rebound tenderness. Then too we have the signs of tenderness in the cul-de-sac and on motion of the cervix, which cannot be dismissed. If we are considering the pelvis and the acute problem, we think

of three systems: the urinary tract, the gastrointestinal tract and the genital tract. I believe that we can rule out the urinary tract. This was not a good history for pyelitis, although we think of that in a person with an early pregnancy. The patient had no fever, the urine was normal, and there was no characteristic radiation of pain and no other data on which to justify that diagnosis.

When we come to the gastrointestinal tract we come to the obvious problem, which I am sure played a large role in the mind of the surgeon taking care of the patient. The thing to rule out — by operation, if necessary — is appendicitis. She did have a short history, with a shift of the pain from generalized abdominal to the right lower quadrant that is one of the cardinal symptoms of appendicitis. She had anorexia, which often occurs instead of nausea and vomiting; thus, one frequently sees acute appendicitis with the patient complaining of not having desire for food that day. On the other hand, nausea and vomiting are expected in an acute appendiceal disease, especially when one is thinking of the acute obstructive type, which is so dangerous. This patient had an elevated white-cell count and localized signs at McBurney's point. Against appendicitis, in addition to the absence of nausea and vomiting, is the absence of bowel symptoms. She had a normal bowel movement on the day before admission and a small one on the previous day that may have been normal. She did not give the history of mild constipation that so regularly goes with an acute appendicitis. The bowels move a little, but there is no satisfactory bowel movement. So much for appendicitis at the moment. Since we do not have to make the final decision, we can assume the academic point of view and say that she did not have enough to go with acute appendicitis. If appendicitis was present, it does not impress one as the acute obstructive type.

One might think of a Meckel's diverticulum, but I rule it out on the basis of the absence of obstructive symptoms and the presence of right-sided localization of the pain.

Gastroenteritis is a common catch-all diagnosis. This patient had neither gastric nor enteric symptoms.

Carcinoma even in this age group is important. We occasionally see carcinoma of the cecum or carcinoid of the appendix that may give this picture and lead to an operation for an acute condition. However, we have no data on which to base that diagnosis. There are other things that we might think of, such as diverticulitis of the cecum and a twisted epiploic appendix, both of which result in prominent bowel symptoms, of which this patient had no complaint.

Turning from the gastrointestinal tract to the pelvic organs, I think that we may find more fertile ground. I would rule out pelvic inflammatory disease. She had no fever, was apparently not very sick and had no profuse menstrual irregularity of flow. She did not have the physical findings to go with it. A twisted cyst of some kind should be considered. The history is compatible with that diagnosis. She had vague, generalized abdominal pain shifting to one side and going low in the abdomen, with a slight suggestion of bowel symptoms but not very much. I assume that if she had a twisted cyst large enough to make her this sick, the cyst would have been palpable. Furthermore, with a twisted cyst I would expect nausea and vomiting. In fact we have expected these symptoms right along but have not observed them.

The one diagnosis that we arrive at is the question of an ectopic pregnancy. Against that diagnosis there is only one real factor and not a really good argument against it. The patient had no bleeding, which is common in ectopic pregnancy. But there is no reason for bleeding irregularly at this point, unless there is rupture of the pregnancy, or leakage. In favor of extrauterine pregnancy are a good many things: the menstrual history and the skipped period, and something happening on one of the expected days of a period, which is not uncommon with ectopic pregnancy. She had the subjective symptoms of pregnancy, tenderness referred to the pelvis, and particularly tenderness on motion of the cervix. A pelvic appendix can also give tenderness on motion of the cervix but the factor *par excellence* that gives such tenderness is a little bleeding behind the uterus in the cul-de-sac or bleeding in one tube with tenderness high up on the right. Because it is high, there could well have been a small swelling in the right tube, which was tender, but could not be nicely delineated as an ovarian tumor.

The whole picture seems to be that of pelvic irritation. The very vague abdominal complaints without subsequent involvement of the gastrointestinal tract point to the uterus or ovaries. As the best possibility I would select ectopic pregnancy, which had just started to abort, causing leakage of blood into the cul-de-sac. The patient had not had a ruptured ectopic pregnancy in the dramatic sense.

A PHYSICIAN: I should like to say that I have seen a very similar picture in a patient who had a fibroma of the uterus that had degenerated.

DR. SCANNELL: I think that is a real possibility, especially with associated pregnancy, although I think that it might be picked up as an irregularity of the uterus on examination.

DR. BARTLETT: I saw this woman shortly after she was admitted and thought that she probably had acute appendicitis. The signs were rather well localized although we realized that they were not very striking. The tenderness was not of great magnitude and the spasm was minimal. We had

the benefit of feeling the uterus, which was large for an ectopic pregnancy and more like that of a normal pregnancy. I was somewhat comforted by the fact that the obstetrician, who was an experienced man, thought that it was a normal intrauterine pregnancy. In any case we could not rule out appendicitis. We operated on her with that preoperative diagnosis.

Clinical Diagnosis

Acute appendicitis.

Dr. Scannell's Diagnosis

Ectopic pregnancy.

Anatomical Diagnosis

Twisted cyst of serosa of cecum.

Pathological Discussion

Dr. Bartlett: When the peritoneum was opened there was a small amount of blood-tinged fluid in the peritoneal cavity. The appendix was normal. The terminal ileum was normal. There were abnormal lymph nodes in the mesentery. We could find no Meckel's diverticulum, and both tubes and ovaries were entirely normal. A low hanging cecum extended down over the pelvic brim and was delivered into the wound. Hanging from the posterior wall behind the base of the appendix was a pedunculated cyst the size of an English walnut. The stalk was about 3 cm. long. The cyst was thin walled and had a 360° twist in its pedicle. The omentum was adherent to the surface of the cyst. Even then we did not know what it was. It was well on in the evening, but Dr. Castleman was in the hospital and he came over and looked at it. The thing that occurred to me was the possibility of some queer second implantation of another ovum, but it did not seem to be that, and Dr. Castleman agreed. The cyst was removed very easily, and the patient made an uneventful recovery.

Dr. Benjamin Castleman: In gross the specimen looked like a paraovarian cyst that had twisted and at the site of the twist was a small hematoma, which resulted from the twist. The wall was thin and contained straw-colored fluid with a bit of hemorrhage in it as a result of the twist. On microscopical examination no definite diagnosis could be made except that of cyst. It probably was congenital in origin. It is conceivable that it might have been an appendix epiploica that had slowly twisted, with resultant central necrosis and cystification. The few twisted appendices epiploicae that I have seen have all been on the left side in the sigmoid, where there are more fat tabs. These, then, are the two possibilities: a congenital rest or a twisted appendix epiploica that had degenerated.

Dr. Bartlett: I have never seen anything like this. I would be interested to know if anyone has seen a cyst of this type arising from the cecum or anywhere in the gastrointestinal tract.

Dr. Falls B. Hershey: Do not ovarian cysts occasionally move from their attachment to the ovary?

Dr. Castleman: It would not have been implanted on the posterior wall of the cecum.

Dr. Hershey: Does a reduplication from that area ever give this picture?

Dr. Castleman: I have never seen one as small as this. It was 2 or 3 cm. in diameter.

Dr. Richard H. Sweet: I have seen cysts arising from embryonic rests in connection with the ovary. I recall a case in this hospital, in which operation was performed by Dr. George A. Leland. It was a sizable cyst, however, ovarian in origin.

Dr. Castleman: There is no evidence for that here.

CASE 34062

Presentation of Case

A sixteen-year-old high-school boy entered the hospital complaining of fever, sweats, aches and pains.

He had been in excellent health all his life until three months before admission, when he first noticed a dull aching pain in the legs and pelvic bones. The pain was mild at first, being present only on walking, and after a week was replaced by a vaguely localized but persistent aching of the right leg, mainly in the muscles rather than in the joints, that was worse at night and not particularly aggravated by motion. The pain was often severe enough to prevent sleeping and, in spite of heat treatments, grew gradually worse. X-ray studies of the spine at that time were negative. The patient was not acutely ill until three weeks before entry, when he was awakened by a severe aching pain across the lower back and was found trembling and perspiring profusely. The following morning the temperature was 100°F. Within two or three days the backache subsided, but he began to notice pleuritic pain in the left anterior portion of the chest and later on the right side as well. He was given sulfonamide tablets for a week but continued to have an irregular fever, the temperature ranging up to 102°F., profuse sweating and generalized muscle aches as well as pleuritic pain. An x-ray film of the chest taken one and a half weeks after the onset of these symptoms was said to show "virus pneumonia." After two weeks the temperature came down somewhat. The patient was then given penicillin in wax on two consecutive days. After each injection the temperature rose higher, and he felt worse. On the day before entry the temperature reached 103°F. There had been no coryza, cough or gastrointestinal symptoms except for anorexia.

Physical examination showed a well nourished boy, who was rather well developed for his age. He seemed inattentive, restless and irritable, but not in distress. The gums were slightly reddened and tender, and the throat was moderately injected. Considerable tenderness was elicited just anterior to the sternomastoid muscles on both sides of the neck. This tenderness seemed to be over several pea-sized, deep lymph nodes. No other adenopathy was noted. The heart was of normal size, with a generalized soft, blowing systolic murmur. The abdomen was normal; the liver and spleen were not palpable.

The temperature was 101.6°F., the pulse 110, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Urinalysis showed a specific gravity of 1.010, a + test for albumin and a 0 test for sugar. The hemoglobin was 10.5 gm., and the white-cell count 3200. The differential count revealed 89 per cent small lymphocytes and 11 per cent "atypical lymphocytes" and no polymorphonuclear leukocytes. The platelets were normal. Widal, Brucella, tularemia and heterophil-antibody agglutinations were negative. An x-ray film of the chest was clear.

In the hospital the patient continued to run a low-grade fever, his condition growing slowly but progressively worse. After two and a half weeks the blood smear showed numerous large cells that were thought to be monoblasts or stem cells. The white-cell count, after an initial drop to 1400, rose steadily to as high as 40,500 after a few weeks. Differential counts continued to show a virtual absence of polymorphonuclears and numerous atypical monocytes and "blast" forms each averaging about 40 per cent of the total. Additional x-ray films of the chest revealed small areas of increased density scattered throughout the lower lobes. This process on repeated x-ray examination seemed to become more marked, and the areas of density somewhat confluent. X-ray studies of the cervical spine and ribs disclosed no definite evidence of bone destruction. During the fourth hospital week x-ray examination of the skull showed a soft-tissue mass in the right frontal area just anterior to the coronal suture. There appeared to be destruction of the outer table underlying it. The patient was given several blood transfusions but failed steadily, and expired approximately five and a half weeks after admission.

Differential Diagnosis

Dr. Bernard M. Jacobson: This case is obviously one of acute leukemia. The initial symptoms in this patient are extremely common in most cases of acute leukemia — namely, those suggestive of infection and bone and joint disease. During the three months before the patient entered the hospital the differential diagnosis could have been extended to a large number of different conditions, including virus infection, rheumatic fever, brucellosis, erythema nodosum, periarteritis nodosa and lupus erythematosus. During the three weeks before entry the patient undoubtedly had pleural or pulmonary infection with regression, as noted by the first normal chest film after entry. We are not told anything regarding the blood picture during these three months, but it is easily imaginable that the blood morphology was nondiagnostic.

After entry the first physical signs that can be related to the later established diagnosis are redness and tenderness of the gums and cervical lymphadenopathy. The soft, blowing systolic murmur does not indicate organic heart disease but is more likely to be due either to the fever or to the anemia. The clinical course included fever and the development of increased areas of infiltrates in both lungs. The last chest film that I viewed appeared to show dilatation of the heart, diffuse pulmonary infiltration and pleural effusion, more marked on the right side. The presence of only minimal lymphadenopathy and the absence of splenomegaly are quite common in acute leukemia.

The initial blood examination revealed an anemia and a leukopenia. Although we are not informed of the course of the hemoglobin this level must have fallen significantly during the remainder of the hospital stay. In most of the smears the red cells were generally slightly macrocytic, with only slight variation in size and shape, and were well filled with hemoglobin. The platelets appeared normal or slightly reduced. The appearance of the red cells is certainly compatible with a myelophthisic anemia.

The most striking laboratory finding is the white-cell picture. I had the opportunity to study six blood smears. The initial smear revealed a majority of the white cells to consist of apparently mature small lymphocytes, but within four days the picture had changed. The remaining smears showed successively large numbers of cells, which varied in size from that of a normal monocyte to two or three times as large as a normal monocyte. Many of the cells showed serrated margins suggestive of pseudopodia. The cytoplasm ranged from lightly basophilic to intensely basophilic, often vacuolated and with or without a moderate number of azurophilic granules. The nuclei of these cells were either round or oval or reniform or even lobulated, with a skein-like coarse chromatin and containing one or more nucleoli. The most mature of these cells appeared to be intermediate between the mature monocytes and the obvious blast forms and can be termed promonocytes. The blast forms with extremely large and serrated margins looked unlike myeloblasts or lymphoblasts and can be called monoblasts. The changes in the white-cell picture during the course of the disease are not uncommon in monocytic leukemia and have recently been well described.*

*Rappoport, A. E., and Kugel, V. H. Monocytic leukemia. *Blood* 2: 332–355, 1947.

Three clinical features of this disease can be readily explained by the diagnosis of monocytic leukemia. The initial bone and joint symptoms were possibly due to leukemic infiltrations of the periosteum or juxta-articular bone of the lumbar spine, pelvis and femurs. The later pulmonary findings are more likely to have been due to leukemic infiltrates rather than to infection. Finally, the soft-tissue mass noted in the right frontal area of the skull was probably also due to a leukemic tumor. Whether this tumor had the appearance of a chloroma or not I cannot predict.

During the early part of the hospital stay the abnormalities of the white cells could have reasonably brought up the question of leukemoid monocytic reaction in various diseases such as tuberculosis, lymphoma, lupus erythematosus and subacute bacterial endocarditis, as well as the monocytic phase sometimes seen in agranulocytosis. The later appearance of numerous blast forms, however, rendered these possibilities extremely unlikely.

In view of the complete absence of myeloblasts and myelocytes in the blood smears I believe that we can dismiss the possibility of the Naegeli type of monocytic leukemia — that is, a variant of myelogenous leukemia.

My diagnosis is acute monocytic leukemia.

DR. LOWREY F. DAVENPORT: It might be well to emphasize the earlier weeks of this patient's illness before abnormal cells appeared in the blood stream. We were confronted with a fever of unknown origin, enlarged cervical lymph nodes and a complete absence of granulocytes. For a time we hoped that the condition was an agranulocytosis following sulfadiazine, which had been given elsewhere. The enlarged cervical lymph nodes and a progressive increase in the mononuclear cells temporarily raised the hope of infectious mononucleosis. In fact we built a very strong circumstantial case on this premise. This boy's roommate had had, two weeks prior to the patient's initial symptoms, an episode of fever with enlarged lymph nodes that could have been infectious mononucleosis. Unfortunately, no blood studies were made. For several weeks, then, we proceeded on the assumption that this more hopeful diagnosis was possible. It was not until the appearance of large numbers of abnormal cells in the peripheral blood that the possibility of an infectious mononucleosis masked by agranulocytosis was dismissed.

CLINICAL DIAGNOSIS

Acute monocytic leukemia.

DR. JACOBSON'S DIAGNOSIS

Acute monocytic leukemia.

ANATOMICAL DIAGNOSES

Lymphatic leukemia.

Leukemic infiltration of bone marrow, spleen, lymph nodes, liver, kidneys, lungs, testicles, pericardium, pleura and voluntary muscle.

Hydrothorax, bilateral, slight.

Ulcers, nonspecific, of esophagus, stomach and small intestine.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This case, as Dr. Davenport pointed out, was very confusing until the blood picture in the last few weeks of life became frankly leukemic. A large proportion of the cells were extremely immature, but the hospital hematologists who saw the smears agreed with Dr. Jacobson that the cells were probably monoblasts. I could reach no other conclusion myself when I reviewed the blood smears. The autopsy findings, however, were inconsistent with a diagnosis of monocytic leukemia, and I am at a loss to explain the discrepancy.

Widespread leukemic infiltration was present in the bone marrow, lymph nodes, spleen, thymus, liver, kidneys, testicles and lungs, as well as many tumor-like masses in skeletal muscles and serosal tissues. None of these tumors had the greenish color of chloromas. The pulmonary infiltration was particularly extensive. It was almost exclusively interstitial but so extensive that the intervening alveoli were completely collapsed and the tissue seemed solidly consolidated.

The problem of the case lies in the nature of the cells composing the infiltrate. They were similar in all areas and appeared in the fixed tissue sections to be characteristic, quite mature lymphocytes. The cells were small, the cytoplasm scanty and basophilic, and the nuclei predominantly round with peripheral chromatin and few conspicuous nucleoli. No cells of the large, very immature type, so numerous in the peripheral blood, were to be found, and very few cells that suggested monocytes in any stage of development were present. I am forced on the basis of the anatomic material to make a diagnosis of lymphatic leukemia, and you will have to choose for yourselves whether to trust the clinical or the anatomic evidence.

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STREPTOMYCIN FOR URINARY-TRACT INFECTIONS

There are now several recognized methods that have been employed with varying success in the treatment of urinary-tract infections. Methenamine with acid phosphate is somewhat effective as a urinary antiseptic. Acidification of the urine with mandelic acid or one of its salts has proved useful in many cases. The sulfonamides, however, have proved much more successful in the simple acute infections. Since gram-positive organisms that are susceptible to penicillin are infrequent as causes of infection of the urinary tract, that antibiotic has only limited uses in this field. On the other hand, streptomycin should prove more useful in the therapy of these infections since it is the most effective agent now available against the gram-negative bacilli that are the predominant bacterial agents in infections of the urinary tract.

The results of streptomycin treatment of urinary-tract infections have not proved universally favorable. In 409 cases collected by the Committee on Chemotherapeutics and Other Agents of the National Research Council,[1] the over-all recovery rate was only 42 per cent. Similar results were obtained in many clinics. Perhaps the most important causes of such failures reside in the nature of the infections that are treated. That is particularly true of chronic cases of pyelonephritis in which there are underlying anatomic defects that interfere with proper drainage, as well as destructive processes that are difficult to heal and remain the source of persistent infection or sites for reinfection. It is just these conditions that also interfere with the success of other forms of therapy that have usually been used without benefit in these cases before streptomycin was tried.

One of the most important causes of streptomycin failures, however, is the rapid replacement of streptomycin-sensitive organisms in the urine by organisms that are highly resistant to streptomycin. In many cases the resistant bacteria have increased more than eight-thousandfold in a matter of a few hours after the first dose of streptomycin was given.[2]

Since the development of resistant bacteria in vitro is usually accomplished by exposing organisms to subeffective concentrations of the antibacterial agent, it is supposed that the use of massive doses of streptomycin would prevent the development of resistant bacteria in the urine. Unfortunately, the range of streptomycin dosage that is feasible in human beings is very narrow, and the upper limit of such doses is not much greater than the amounts that are therapeutically effective. The use of maximum doses, therefore, has not proved successful in preventing the appearance of resistant strains that interfere with the efficacy of therapy.[2]

Alkalinization of the urine, however, has proved extremely useful in this respect. It has been shown that within the range of reaction attainable in the urine — namely, between pH 5.5 and 8.0 — the antibacterial effect of any given concentrations of streptomycin may be increased up to eightyfold.[3] A

given dose of streptomycin can, therefore, be made more effective, at least in the urine, by administering alkalis in quantities adequate to render and keep the urine alkaline. A given dose of streptomycin may then be as much as eighty times as effective at pH 8.0 as at pH 5.5 or, put another way, if the urine is kept alkaline between pH 7.5 and 8.0, the amount of streptomycin given may be equivalent in its antibacterial action to as much as eighty times the same dose were it given during a time when the urine was kept acid between pH 5.5 and 6.0.

That this factor is actually of practical importance in increasing the effect of streptomycin in the therapy of urinary-tract infections has been shown by clinical results. Failures have been infrequent, and the appearance of resistant strains is rarely encountered in cases in which the urine has been kept alkaline during streptomycin therapy,[4, 5] whereas the rapid development of resistant strains has been very frequent when the urine is acid as it usually is in most cases of urinary-tract infections other than those due to urea splitters. Furthermore, in most of the failures or relapses, the infections that later occur have been proved to be due to new strains of bacteria not previously present and also sensitive to streptomycin.

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TRICHINOSIS AND FOOD CONSERVATION

Misinterpretation of the plea of the national food conservation committee not to overcook meat could easily cause an increase in trichinosis and perhaps some forms of food poisoning. Evidence that the problem of trichinosis is already large enough is presented elsewhere in this issue of the *Journal*. The practice of undercooking pork and pork products is widespread enough for perhaps hundreds of persons to become infested with the parasites in Massachusetts annually. Nothing should be done to increase the magnitude of the trichinosis problem.

The prevalence of salmonellosis may also be increased by undercooking animal products. Salmonella organisms are present in many animals, as well as in eggs and other products. Heating thoroughly is the best safeguard against such infections. Heating a large roast, ham or fowl all the way to the center takes longer than many cooks and housewives realize, however. Even two hours of boiling of a large ham does not always raise the center to a high enough temperature (at least 150°F.) to kill salmonella organisms.

Palatability and nutritional value are important features to be preserved but it is hoped that they will not be purchased at the price of increased illness. It is essential to emphasize that meats should not be undercooked while efforts are made not to overcook them.

FRANCES STERN

The country lost one of its outstanding workers in a line ancillary to medicine in the death, on December 23, 1947, of Frances Stern. Miss Stern, the daughter of refugees from German persecution who came to this country in 1848, was born seventy-four years ago in Boston's South End. In the same section of the city she spent her life in social work beginning in 1895, when, with Miss Isabel R. Hyams, she was founder and co-director of the Louisa Alcott Club, devoted to teaching nutrition and homemaking to children.

A graduate of the Garland Kindergarten Training School in 1897, Miss Stern became a special student at the Massachusetts Institute of Technology in 1913 and at the London School of Economics in 1922. From 1918 to 1921 she was director of an American Red Cross clinic for children in Paris. As a result of her settlement-house work in Boston her appreciation of the economic and moral importance of proper nutrition developed. On July 2, 1943, on Miss Stern's seventieth birthday, the Food Clinic at the Boston Dispensary, which she had founded in 1918, was named in her honor, and the Frances Stern Nutrition Fund for Tufts College Medical School was established.

The Dispensary Food Clinic, at the time of its establishment, was a unique experiment of its kind and has been the model for over fifty similar clinics that have been set up throughout the world. Here patients have learned the bearing of diet on their individual health problems, with consideration given to their religious and racial backgrounds and their economic situations.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

MANSFIELD — James A. Mansfield, M.D., of Boston, died on June 29. He was in his eighty-first year.
Dr. Mansfield received his degree from Jefferson Medical College of Philadelphia in 1896.
A son survives.

POLIAK — Mendel Poliak, M.D., of Springfield, died on September 15. He was in his sixty-first year.
Dr. Poliak received his degree from Université de Montpellier Faculté de Médecine in 1922. He was a member of the staff of Wesson Memorial Hospital.

RICKER — Carroll H. Ricker, M.D., of Worcester, died on September 6. He was in his eightieth year.
Dr. Ricker received his degree from Tufts College Medical School in 1907. He was a member of the staff of Worcester City Hospital and was a fellow of the American Medical Association.
His widow and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TRICHINOSIS IN MASSACHUSETTS

The problem of trichinosis is much larger than is generally realized. In the ten-year period 1936–1945, a total of 287 cases were reported to the Massachusetts Department of Public Health with 7 deaths. Cases have been reported with regularity from all areas, a total of eighty-one different communities reporting one or more cases during the ten-year period. However, there can be little doubt that many times as many persons were so mildly ill of trichinosis as never to have come under medical care.

Surveys of autopsy material in various localities throughout the United States have shown an incidence of trichinous infections varying from 16 to 36 per cent. It is generally recognized that man becomes infected by eating trichinous pork, which in turn comes from hogs fed on garbage containing scraps of uncooked trichinous pork. The average incidence of trichinosis among hogs in the United States during the past fifty years has remained practically unchanged at a level of approximately 1.5 per cent. It has been estimated that 96,849,000 hogs were slaughtered in the United States during 1944, and the total production of pork was 12,893,000,000 pounds.

This amount of pork would furnish about 30,000,000,000 individual servings, or approximately 200 servings per person in the United States, of which 3 would contain trichinae. Since the average length of life of Americans is now over sixty-four years and an average of 200 servings of pork are annually eaten per person, for the lifetime of each person nearly 200 meals of pork containing trichinae are consumed.

Another way of visualizing the magnitude of the problem in Massachusetts is to estimate the number of persons acquiring the parasites. Each year about 70,000 persons are added to the population by births. Even at the lowest estimate 16 per cent of this number, or 11,200, should show symptoms each year instead of the average of less than 30 cases actually reported annually during the last ten years.

The onset of the illness is of variable intensity, depending upon the amount of infected meat eaten and the abundance of trichinae in the meat. The first symptoms are generally gastrointestinal, consisting of nausea, vomiting, abdominal pain and diarrhea lasting for three to five days. These are followed by a period of muscular aching, pain and tenderness, chills, a temperature not unlike that in typhoid fever, cough, edema of the eyelids and skin rash. Not infrequently, signs and symptoms of pulmonary, cardiac and central-nervous-system involvement are found. This period of peripheral symptomatology lasts as long as the adult worm is producing larvae — five to seven weeks. Death occurs most frequently from the third to the sixth week. Although recovery is usually complete, vague rheumatic pains may persist for about a year.

The most frequent laboratory aid is the elevated eosinophil count. The precipitin test is highly sensitive but is negative early in the illness, three to four weeks often being required before it is elevated. The skin test is of value if there is first an initial negative response followed by a positive reaction at a later date. Muscle biopsy, if positive, makes the diagnosis certain.

Various measures have been advocated in the control of trichinosis, including destruction of rats, elimination of garbage and offal from the feed of hogs, cooking of garbage to be fed to hogs, proper processing of pork products customarily eaten without cooking, microscopical inspection of pork and education of the public in the necessity of adequately cooking pork and pork products.

Processing of pork and its products means the treatment by freezing, cooking, smoking, curing or other methods that will render nonviable any trichinae present in the meat. Cooking and freezing are the easiest and most readily accessible methods. Trichinae are killed at a temperature of 55°C. (131°F.). Federal regulations require that, in the killing of trichinae by heat, all parts of the meat be raised to a temperature of 58.33°C. (137°F.); the American Public Health Association recommends

that all fresh pork and its products be cooked at a temperature and for a time sufficient to allow all parts of the meat to reach a temperature of at least 65.6°C. (150°F.).

Trichinous meat in sections of 15 cm. or less can be rendered noninfectious by refrigeration at a temperature of 5°F. (—15°C.) for twenty days, —10°F. (—23.3°C.) for ten days or —20°F. (—30°C.) for six days. It has also been found that raw pork in commercial quantities may be rendered free of infective trichinae by reduction of its temperature to —35°C. (—31°F.) for a short time or by freezing at —17.8°C. (0°F.) for seventy-two hours. In ground meat, encysted trichinae are killed in a few minutes at a temperature of —17.8°C. (0°F.). In most deep-freezing cabinets, such as those used in the home, temperatures varying from 0 to 5°F. are usually maintained, and thus another method of assuring trichina-free meat has become available to the individual consumer.

Recently the President's committee for the conservation of food recommended that meat should not be overcooked. However, it is important that the consumer should not go to the other extreme of undercooking meat, particularly pork and its products, unless he is unreservedly certain that it has been properly processed beforehand.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1947

Résumé

Disease	December 1947	December 1946	Seven-Year Median
Chancroid	6	0	2*
Chicken pox	1680	1337	1444
Diphtheria	37	87	21
Dog bite	620	556	517
Dysentery, bacillary	19	4	12
German measles	64	67	68
Gonorrhea	262	316	316
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	2	0	0*
Malaria	7	7	7
Measles	459	840	840
Meningitis, meningococcal	1	9	12
Meningitis, Pfeiffer-bacillus	8	8	3
Meningitis, pneumococcal	3	7	7†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	0	0	1†
Meningitis, undetermined	5	2	2†
Mumps	1267	318	670
Pneumonia, lobar	96	114	232
Poliomyelitis	7	17	11
Salmonellosis	9	10	5
Scarlet fever	475	664	978
Syphilis	274	238	376
Tuberculosis, pulmonary	226	207	207
Tuberculosis, other forms	14	13	13
Typhoid fever	4	3	4
Undulant fever	4	2	3
Whooping cough	682	730	730

*Three-year median.

†Five-year median.

Comment

Diseases above the seven-year median are chicken pox, diphtheria, dog bite, bacillary dysentery, mumps and salmonellosis.

Diseases below the seven-year median are lobar pneumonia, measles, meningococcal meningitis, poliomyelitis and scarlet fever.

Chicken pox showed a marked increase in December, bringing the year's total to the second highest since 1916. Mumps reached the highest peak of the year in December, which probably indicates that 1948 will be a mumps year. The seasonal increase in diphtheria continues, returning to the level of the late spring of 1947.

Only one case of meningococcal meningitis was reported after seven years of high prevalence in which 60 cases were once reported in December.

Scarlet fever dropped to the second lowest level ever reported, the total for 1947 being the lowest since 1905. Although the incidence of measles is low, the usual seasonal increase has brought the total to three times the number of cases reported for November.

Geographical Distribution of Certain Diseases

Anthrax was reported from: Franklin, 1; total, 1.

Diphtheria was reported from: Bedford, 1; Boston, 9; Brookline, 5; Chelsea, 2; Chicopee, 1; Everett, 1; Holyoke, 2; Malden, 2; Revere, 8; Somerville, 6; total, 37.

Dysentery, bacillary, was reported from: Clinton, 1; Greenfield, 1; Salem, 1; Swampscott, 3; Worcester, 13; total, 19.

Malaria was reported from: Boston, 1; Lawrence, 1; Marion, 1; Medford, 2; Northampton, 1; Uxbridge, 1; total, 7.

Meningitis, meningococcal, was reported from: Worcester, 1; total, 1.

Meningitis, Pfeiffer-bacillus, was reported from: East Longmeadow, 1; Everett, 1; Lawrence, 2; Quincy, 2; West Springfield, 1; Worcester, 1; total, 8.

Meningitis, pneumococcal, was reported from: Cambridge, 1; Holliston, 1; Pittsfield, 1; total, 3.

Meningitis, undetermined, was reported from: Boston, 1; Pittsfield, 1; Somerville, 1; Springfield, 1; Worcester, 1; total, 5.

Poliomyelitis was reported from: Cambridge, 1; Framingham, 1; Northampton, 1; Rockland, 1; Sherborn, 1; Southboro, 1; Worcester, 1; total, 7.

Salmonellosis was reported from: Belmont, 1; Cambridge, 4; Montague, 1; New Bedford, 1; Revere, 1; Swampscott, 1; total, 9.

Septic sore throat was reported from: Boston, 1; Merrimac, 3; Milton, 1; total, 5.

Trachoma was reported from: Worcester, 1; total, 1.

Trichinosis was reported from: Cambridge, 2; Pittsfield, 1; Salem, 1; Stoneham, 1; total, 5.

Typhoid fever was reported from: Boston, 1; Fall River, 2; Newton, 1; total, 4.

Undulant fever was reported from: Attleboro, 1; Boston, 1; Danvers, 1; Rutland, 1; total, 4.

MISCELLANY

SCHOLARSHIPS FOR NURSES

The Greater Boston Nursing Council recently announced that scholarships and loan funds for students are available at the nurses' training schools of the following institutions: Beth Israel Hospital; Mt. Auburn Hospital; Children's Hospital; Faulkner Hospital; Massachusetts General Hospital; Massachusetts Memorial Hospitals; New England Deaconess Hospital; Newton-Wellesley Hospital; Peter Bent Brigham Hospital; Simmons College; Boston College; Melrose Hospital; and New England Hospital for Women and Children.

NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Frederick Chapman Robbins, of Bronxville, New York (A.B. University of Missouri 1936; M.D. Harvard University 1940), assistant in pediatrics; Henry Mitchell Putnam of Westwood (Ph.B. Yale University; M.D. Harvard University 1935), assistant in pediatrics; Walter Higbee Caskey, of Cambridge (M.D. Harvard University 1946), research fellow in comparative pathology and tropical medicine; Victor Clarence Vaughn, III, of Richmond, Virginia (A.B. Harvard University 1939; M.D. Harvard University 1943), research fellow in pediatrics; Samuel Waldfogel, of Detroit, Michigan (S.B. Wayne University 1938; M.A. University of Michigan 1939; Ph.D. University of Michigan 1946), research associate in psychiatry; Ronald Charles Sniffen, of Milton (M.D. University of Toronto 1936), instructor in pathology; Edgar Breck Taft, of Cambridge (M.D. Yale University School of Medicine 1942), instructor in pathology; Dante Francesco Campagna-

Pinto, of Cambridge (A.B. Harvard University 1939; M.D. Harvard University 1943), assistant in pathology; John Merrill Craig of Berkeley, California (A.B. University of California, 1936; M.A. University of California 1938; M.D. Harvard University 1941), assistant in pathology; Melvin Bertram Black, of Boston (A.B. Harvard University 1940; M.D. Harvard University 1943), research fellow in pathology; Gilcin Finley Meadors, Jr., of Washington, D. C. (S.B. Millsaps College 1936; M.D. Tulane University of Louisiana 1940; M.P.H. Johns Hopkins School of Public Health and Hygiene 1947), instructor in preventive medicine; John Platt Hubbell, Jr., of Brookline (A.B. Williams College 1940; M.D. Harvard University 1943), assistant in pediatrics; Donald Emerson McLean, of Winchester (A.B. Harvard University 1938; M.D. Harvard University 1943), assistant in pediatrics; Harold Edelhoch, of Bronx, New York (A.B. New York University 1943; A.M. Princeton University 1946; Ph.D. Princeton University 1947), research fellow in physical chemistry; Drummond Ellis of Glasgow, Scotland (B.Sc. Glasgow University 1944), research fellow in physical chemistry; James Alexander Wolff, of Boston (A.B. Harvard University 1935; M.D. New York University College of Medicine 1940), research fellow in pediatrics; Arthur Francis Battista, of Ontario, Canada (B.Sc. McGill University 1943; M.D.C.M. McGill University 1944; M.Sc. University of Western Ontario 1947), research fellow in physiology; Harold Scarborough, of West Yorkshire, England (M.B., Ch.B. University of Edinburgh, Scotland 1932; Ph.D. University of Edinburgh, Scotland 1938), research fellow in physiology; Melvin Hyman Kaplan, of Cambridge (A.B. Harvard University 1942), Harold C. Ernst, fellow in bacteriology and immunology; Doreen Nightingale, of London, England (M.R.C.S., L.R.C.P. University College Hospital Medical School 1939; M.B., B.S. Lond. University College Hospital Medical School 1940; M.S. Lond. and F.R.C.S. England 1945), research fellow in surgery; John Butler Tomkins, of Waverley (S.B. Wesleyan University 1926; M.D. Tufts College Medical School 1935), instructor in psychiatry; and Jacques Lewin, of Paris, France (M.D. Faculté de Médecine, Paris 1929; Licencie en Sciences, Faculté des Sciences, Paris 1933; M.D. [Dipl. d'État] Faculté de Médecine, Paris, 1947), research fellow in physical chemistry.

NATIONAL INSTITUTE OF HEALTH

Establishment of an experimental-biology and medicine institute, in the National Institute of Health of the United States Public Health Service, has been announced. The new research institute will combine the functions of the Division of Physiology and the Pathology and Chemistry Laboratories and will permit greater co-ordination of scientific investigations.

Dr. William Henry Sebrell, Jr., chief of the Division of Physiology, has been named director of the new Institute and he will also serve as associate director of the National Institute of Health.

Formation of the Institute is part of a wider organization of the National Institute of Health, according to Dr. Thomas Parran, surgeon general of the Public Health Service. Four other divisions and laboratories engaged in scientific research will also be consolidated into two additional institutes, all of which will be modeled after the National Cancer Institute.

BAY STATE SOCIETY FOR CRIPPLED AND HANDICAPPED

The Bay State Society for the Crippled and Handicapped has made a grant of $12,000 for the work of the Seizure Unit of the Neurological Institute at the Children's Medical Center in Boston.

HOSPITAL SURVEY AND CONSTRUCTION ACT

As of January 9, according to the Washington Report on the Medical Sciences, 92 applications for construction of hospitals, dispensaries and health centers under the Hill–Burton Hospital Survey and Construction Act has been approved. The estimated outlay will be $40,765,702, of which the Federal Government will provide $13,381,548. The states so far included in the list are Alabama, Florida, Illinois, Indiana, Kentucky, Mississippi, New Mexico, North Carolina, Oklahoma and Texas.

CORRESPONDENCE

SHORTAGE OF NURSES

To the Editor: I read with interest the editorial, "Shortage of Nurses," which appeared in the January 1 issue of the *Journal*.

You may know that House Bill 90, which has been filed with the 1948 General Court of Massachusetts, if enacted, would permit registration by women at the age of twenty rather than twenty-one, a point discussed in the editorial.

In the light of information obtained by our Personnel Policies and Practices Committee, we question the statement that the average nurse in Massachusetts works only a forty-four-hour week. There is a trend in that direction, but statistics show forty-eight hours to be the average work week in this area.

We thank you for the editorial and the points made in it, especially your plea "to exert every effort to obtain for nurses their proper recognition and economic stability."

HELENE G. LEE, *Executive Secretary*
Massachusetts State Nurses Association
420 Boylston Street
Boston

FURTHER NOTES ON FOLIC ACID

To the Editor: It has been a great help to me to have been able to follow, through the many articles published in the 1947 issues of the *Journal*, the conflicting studies on the use of folic acid in the deficiency syndromes associated with macrocytosis of the red cells. I am referring in particular to the two progress reports, "Hematology," by Dr. William Dameshek in the September 18 and 25 issues and the more recent ones on "Pteroylglutamic Acid and Related Substances" by Dr. Frederick Sargent, II, in the October 30 and November 6 issues.

The consensus seems to be that folic acid and related substances help in the control of the two manifestations of deficiency syndromes associated with macrocytosis of the red cells — namely, changes in the gastrointestinal tract and changes in the blood and blood-forming organs — but that folic acid has no influence on the third manifestation, changes in the central nervous system, which is the most serious with the resulting subacute combined degeneration of the spinal cord.

Words of warning on the use of folic acid even for the control of the first two manifestations of the deficiency syndrome have been sounded. I refer in particular to the opinion of Dr. Russel L. Haden, of the Cleveland Clinic who wrote, in an article entitled "Treatment of Pernicious Anemia" (*Postgraduate Medicine* 1:131-135, 1947) that he was relying on liver extract for the present, because folic acid in his opinion had as yet an undetermined place in treatment. More recently, in the Boston issue (September, 1947, number) of the *Medical Clinics of North America*, Drs. Helen W. Belding and Joseph F. Ross, in an article entitled "Recent Advances in Hematology," have stressed the very definite therapeutic limitations of folic acid in the deficiency syndrome associated with macrocytosis. The fact that folic acid is an effective hematopoietic agent in the anemia characterized by macrocytosis and a megaloblastic bone marrow is not denied, but the authors stress what is the most important point in my opinion: that folic acid not only has little influence in altering the changes in the central nervous system but also is unable to prevent them from developing, even though the hematologic status remains normal. More recently, another warning of disastrous consequences has been given against the use of folic acid even in the control of the changes in the gastrointestinal tract and in the blood and blood-forming organs, in spite of the many articles in the recent literature regarding its efficacy in the control of these two manifestations of the deficiency syndrome associated with macrocytosis. Dr. O. C. Hansen-Pruss, in an article entitled "Relapse of Patients with Pernicious Anemia Receiving Folic Acid" (*American Journal of the Medical Sciences* **214**:465-468, 1947) reports 2 patients who were suffering from pernicious anemia and relapsed while receiving folic acid; these patients responded well to liver extract.

It seems to me as a practicing physician that, in answer to the patient with the deficiency syndrome associated with macrocytosis who demands the use of the new drug that has

appeared on the medical horizon, I should reply after analyzing the data submitted to you that by using folic acid he would in the light of present knowledge be taking considerable risk and be spending considerable money, whereas by taking liver extract he would be obtaining sure and proved control and at the same time be saving considerable money.

GABRIEL F. GRECO, M.D.

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BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Methods of Vitamin Assay. Prepared and edited by The Association of Vitamin Chemists, Incorporated. 8°, cloth, 189 pp. New York: Interscience Publishers, Incorporated, 1947. $3.50.

This standard manual was compiled by a committee of scientists recognized as authorities in vitamin research, with the assistance of a large staff of competent reviewers who were not members of the Association. The scope of the book is limited, since only such methods are included as have been successfully used by several committee members, thus representing the combined knowledge and experience of many persons. Special chapters are devoted to each of the important vitamins, and each chapter concludes with a selected list of references to the vitamin under discussion. The manual is recommended as a reference source for all medical and laboratory libraries.

The American Illustrated Medical Dictionary: A complete dictionary of the terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology, medical biography, etc., with the pronunciation, derivation, and definition. By W. A. Newman Dorland, A.M., M.D. Twenty-first edition. 8°, cloth, 1660 pp., with 880 illustrations. With the collaboration of E. C. L. Miller, M.D. Philadelphia: W. B. Saunders Company, 1947. $8.50.

This standard, authoritative dictionary, last published in 1944, has been revised to include the voluminous medical terminology resulting from the research of the war years. In addition to the actual war medicine and surgery, new words have been added in the fields of tropical medicine; aviation medicine; medical zoology and mycology; biochemistry and pharmacology, including antibiotics, enzymes, vitamins and endocrines; and physics and nucleonics, including the application of radioactive isotopes. The names of proprietary medicines have been reviewed, and obsolete terms have been eliminated from the present edition. The book is well published in every way and should be in all medical and public libraries and institutions and also is recommended to all physicians and persons needing an up-to-date medical dictionary.

NOTICES

ANNOUNCEMENTS

Dr. Thomas J. Anglem and Dr. Knowles B. Lawrence announce the association with them of Dr. Martin L. Bradford in the practice of general surgery at 1180 Beacon Street, Brookline.

Dr. Bernard Bloom announces the opening of his office for the practice of urology at 67 Chestnut Street, Springfield.

Dr. Kurt H. Thoma announces the association of Dr. Daniel J. Holland, Jr., in the practice of oral surgery, and the removal of their offices to 1180 Beacon Street, Brookline.

Dr. Robert S. Thomson announces the removal of his office for the practice of general surgery to 866 Main Street, Fitchburg.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The winter meeting of the Massachusetts Medico-Legal Society will be held in the George Burgess Magrath Library, Department of Legal Medicine, Harvard Medical School, on Wednesday, February 11, at 2:30 p.m.

PROGRAM

Business Meeting.
Beryllium Pneumoconiosis. Walter W. Jetter, M.D.
Blood Concentrations of Barbiturates in Relation to Toxic Effects. R. S. Fisher, M.D., and J. T. Walker, Ph.D.
Multiple Foci of Acute Myocardial Necrosis Resulting from Systemic Anoxia. Richard Ford, M.D.
Collation.

FELLOWSHIPS IN PUBLIC HEALTH

Fellowships leading to a master's degree in public health in the field of health education are again being offered to any qualified United States citizen between the ages of twenty-two and forty.

Candidates must hold a bachelor's degree from a recognized college or university at the time the application is filed, and must be able to meet the entrance requirements of the accredited school of public health of their choice. Proof of acceptance at such a school must be furnished before applications are submitted to the Fellowship Awards Committee for consideration. In addition to the bachelor's degree, courses in the biologic sciences, sociology and education are required. Training in public speaking, journalism and psychology and work in public health or a related field are considered desirable.

The fellowship consists of eight or nine months of academic work, which begins with the fall term in 1948, and three months of supervised field experience in community health-education activities in a local health department. The academic training includes courses in public-health administration, epidemiology, public-health and school education, problems in health education, community organization, information technics and others.

Information and application blanks may be obtained from the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

The annual meeting of the American Association of Pathologists and Bacteriologists will be held at the Jefferson Medical College, Philadelphia, on Friday and Saturday, March 12 and 13. Half a day will be devoted to a consideration of "Diseases of Bones." Contributions to this symposium are invited, but all material should reach the Secretary not later than Saturday, February 14. All papers, including illustrative material, must be presented within a limit of ten minutes.

Further information may be obtained from the Secretary, American Association of Pathologists and Bacteriologists, 2085 Adelbert Road, Cleveland 6, Ohio.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

THURSDAY, FEBRUARY 12

FRIDAY, FEBRUARY 13
*9:00-10:00 a.m. Recent Advances in Our Knowledge of Blood Coagulation. Dr. Benjamin Alexander. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, FEBRUARY 16
*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

(*Notices concluded on page xiii*)